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=> s fusion protein
L1 213649 FUSION PROTEIN

=> s l1 and notch ligand
L2 51 L1 AND NOTCH LIGAND

=> s l2 and superantigen
L3 1 L2 AND SUPERANTIGEN

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L3 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2007 ACS on STN
2003:118018 Document No. 138:168835 Targeting of an antigen presenting cell (APC) with a modulator of T cell signalling, such as a **Notch ligand**, coupled to the MHC class II-binding motif from a **superantigen**. Bodmer, Mark William; Champion, Brian Robert; McKenzie, Grahame James; Nye, Lucy Emma (Lorantis Limited, UK). PCT Int. Appl. WO 2003012111 A2 20030213, 93 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-GB3381 20020725. PRIORITY: GB 2001-18155 20010725.

AB The present invention relates to the concept of delivering a modulator of T cell signaling, such as a **Notch ligand**, to an antigen presenting cell (APC). The targeting approach disclosed uses, for example, the major histocompatibility complex (MHC) class II binding motif from a **superantigen** coupled to a modulator of the Notch signaling pathway. **Superantigens** bind both MHC class II mols. and subsets of T cell receptors and thus effectively cross-link APCs to T cells and activate cells polyclonally. The mol. regions of these mols. that impart T cell receptor (TCR) and MHC class II binding have been defined structurally and have been shown to be distinct regions of the mol. By using the MHC class II binding domain with a modulator of the Notch signaling pathway we can focus the activity of the Notch signaling

pathway modulator to the APCs at the site of delivery. Further, the domain lacks toxin activity because it cannot find the T cell receptor to activate T cells. According to one aspect of the present invention there is provided a conjugate comprising a first and a second sequence wherein the first sequence comprises a polypeptide which is capable of binding to an APC, or a polynucleotide encoding therefor, and the second sequence comprises a polypeptide comprising a modulator of a signaling pathway in a T cell or a polynucleotide encoding therefor.

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PROCESSING COMPLETED FOR L2
L4 44 DUP REMOVE L2 (7 DUPLICATES REMOVED)

=> s l4 adn notch ligand DSL domain
MISSING OPERATOR L4 ADN
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s l4 and DSL domain
L5 11 L4 AND DSL DOMAIN

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L6 11 DUP REMOVE L5 (0 DUPLICATES REMOVED)

=> d l6 1-11 cbib abs

L6 ANSWER 1 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN
2006:559208 Document No. 145:61476 Modulators of Notch signaling and cytokine expression for immunotherapy of inflammation and autoimmune disease. Champion, Brian Robert; Young, Lesley Lynn; Mckenzie, Grahame James (UK). U.S. Pat. Appl. Publ. US 2006128619 A1 20060615, 92 pp. (English). CODEN: USXXCO. APPLICATION: US 2005-178724 20050711. PRIORITY: GB 2003-428 20030109; WO 2004-GB21 20040109.
AB The invention provides a method for modifying IL-4 expression in a cell using a modulator of Notch signaling. It also provides methods for generating immune modulatory cytokine profiles with increased IL-4 expression and/or increased IL-10 expression and/or reduced IL-5, IL-13 and TNFα expression. In addition, the invention provides a method for increasing a TH2 immune response and/or decreasing a TH1 immune response in a cell, using a modulator of Notch signaling. The modulators of Notch signaling comprise Notch receptor agonists or antagonists, particularly **fusion proteins** comprising DSL or EGF domains from Delta or Jagged proteins and an Ig Fc segment. Alternatively, the modulator of Notch signaling comprises a Notch intracellular domain. The invention also claims polynucleotides encoding modulators of Notch signaling. Methods of the invention are claimed for use in treating inflammation or an autoimmune condition. In the examples, modulation of cytokine production in mouse and human CD4+ cells by soluble or immobilized human Delta 1 extracellular domain-IgG4Fc **fusion protein** was measured. Expression of IL-10, IFN-γ, and transcription factors Tbet, c-Maf, and GATA-3 was measured in anti-CD3/28 activated mouse T cells under neutral, TH1, or TH2 culture conditions after treatment with the Delta1-Fc protein.

L6 ANSWER 2 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN
2005:387813 Document No. 142:446015 **Notch ligands** by Delta 1 or Serrate 1 reducing peripheral immune responses for therapeutic uses. Lamb, Jonathan Robert; Dallman, Margaret Jane; Hoyne, Gerard Francis (Lorantis Limited, UK). U.S. US 6887475 B1 20050503, 95 pp., Cont.-in-part of Appl. No. PCT/GB97/03058. (English). CODEN: USXXAM.

APPLICATION: US 1999-310685 19990504. PRIORITY: GB 1996-23236 19961107; GB 1997-15674 19970724; GB 1997-19350 19970911; WO 1997-GB3058 19971106.

AB The present invention relates to the use of therapeutic compds. in the modification of T-cells, T-cell-antigen presenting cell (APC) interactions and the interaction between pathogenic organism and immunocompetent cells of a host. In particular, it relates to the use of these compds. in the modulation of the interaction between Notch proteins and their ligands and to the use of such compds. in the therapy of conditions such as graft rejection, autoimmunity, allergy, asthma and infectious diseases.

L6 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN

2004:857429 Document No. 141:325713 Notch signalling modulation using a KLF and its effectors, diagnostic assays and therapeutics for autoimmune and inflammatory disorders. Champion, Brian Robert; Lioumi, Maria; McKenzie, Grahame James; Young, Lesley Lynn (Lorantis Limited, UK). PCT Int. Appl. WO 2004087195 A2 20041014, 150 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-GB1379 20040329. PRIORITY: GB 2003-7472 20030401.

AB A method is described for detecting, measuring or monitoring Notch signalling by determining the amount of a KLF (Kruppel-like factor) protein, or determining the amount of a polynucleotide coding for KLF. Methods of modulating the immune system by modulation of KLF activity and methods of modulating immune cell quiescence and proliferation are also described. A preferred KLF is human KLF-2, also known as LKLF (Q9Y5W3, NM_016270). Modulators of the Notch signalling pathway also comprise **Notch ligands**, such as Delta or Jagged, and DSL, EGF-like or extracellular domains thereof and polynucleotides coding for such proteins. Sequences of Delta-1/Ig-Fc **fusion proteins** are provided. Notch signaling pathway modulation was demonstrated in mouse model.

L6 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN

2004:718374 Document No. 141:242022 Modulators of Notch signalling and of immune cell costimulatory activity for immunotherapy of inflammation, asthma, allergy, transplant rejection, graft versus host disease or autoimmune disease. Champion, Brian Robert; Lioumi, Maria; McKenzie, Grahame James (Lorantis Limited, UK). PCT Int. Appl. WO 2004073732 A1 20040902, 157 pp. DESIGNATED STATES: W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, ML, MR, NE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-GB668 20040218. PRIORITY: GB 2003-3663 20030218.

AB A method is described for detecting, measuring or monitoring Notch signaling by determining the amount of an immune cell costimulatory protein, polypeptide or polynucleotide or determining the amount of a polynucleotide coding for such a protein or polypeptide. The Notch signaling modulators of the invention comprise **Notch ligand DSL domain** or intracellular domain. The immune cell costimulatory

proteins are CD28, CD80, CD86, CTLA-4, ICOS, ICOS ligand, CD40, CD40L, PD-1, PD-L1, PD-L2, OX40 or OX40L. Methods of modulating the immune system are also described. The Notch signaling modulators and the immune cell costimulatory activity modulators are useful for increasing or reducing immune response against cancer or inflammation, allergy, asthma, graft vs. host disease, autoimmune disease and transplant rejection.

L6 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN
2004:610096 Document No. 141:156082 Methods for use of Notch signaling for modulation of cytokine production in T cells and therapeutic uses thereof. Champion, Brian Robert; Young, Lesley Lynn; McKenzie, Grahame James (Lorantis Limited, UK). PCT Int. Appl. WO 2004062686 A2 20040729, 149 pp. DESIGNATED STATES: W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GH, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ. (English). CODEN: PIXXD2. APPLICATION: WO 2004-GB21 20040109. PRIORITY: GB 2003-428 20030109.
AB The invention provides methods for use of modulators of Notch signaling to regulate interleukin 4 expression and T cell immune responses. The invention further claims use of the methods for immunotherapy, to modify the TH1/TH2 balance of an immune response in favor of a TH2 response, by treatment of patient's cells in vivo or ex vivo. In the examples of the invention, a **fusion protein** comprising the extracellular domain of human Delta1 ligand fused to the Fc domain of human IgG4 was immobilized in microtiter plates via its Fc domain. CD4-pos. cell were cultured in the presence of the above **fusion protein**, stimulated with anti-CD28 antibody, and analyzed for cDNA expression by PCR. The CD4+ cells were restimulated in various ways and the cytokines IL-10 and interferon-γ were measured. **Notch ligand** signaling was also measured using a luciferase reporter construct in CHO cells cocultured with recombinant CHO cells expressing Delta1 ligand on the surface. Cytokine production was measured in stimulated mouse CD4+ cells under polarizing conditions. Transcription factor and cytokine expression by anti-CD3/28 activated mouse T cells activated under neutral, Th1, or Th2 culture conditions was measured with or without Delta1 protein.

L6 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN
2004:589350 Document No. 141:145678 Particle-bound modulators of the Notch signaling pathway for use in the treatment of disorders of the immune system. Bodmer, Mark William; Briend, Emmanuel Cyrille Pascal; Champion, Brian Robert; Lennard, Andrew Christopher; McKenzie, Grahame James; Tugal, Tamara; Ward, George Albert; Young, Lesley Lynn (Lorantis Limited, UK). PCT Int. Appl. WO 2004060262 A2 20040722, 294 pp. DESIGNATED STATES: W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GH, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ. (English). CODEN: PIXXD2. APPLICATION: WO 2004-GB46 20040107. PRIORITY: GB 2003-234 20030107; GB 2003-1519 20030123; GB 2003-1510 20030123; GB 2003-1512 20030123; GB 2003-1522 20030123; GB 2003-1524 20030123; GB 2003-1521 20030123; GB 2003-1518 20030123; GB 2003-1515 20030123; GB 2003-1513 20030123; GB 2003-1529 20030123; GB 2003-1526 20030123; GB 2003-1527 20030123; GB 2003-6621 20030322; WO 2003-GB1525 20030404; GB 2003-12062 20030524; WO 2003-GB3285 20030801; GB 2003-23130 20031003.
AB Modulators of Notch signaling are immobilized on pharmaceutically acceptable carriers for therapeutic use in the treatment of immune

disorders. Two derivs. of the **Notch ligand** Delta were prepared: a **fusion protein** with IgG4 and a cysteine-rich derivative These were immobilized on Dynabeads or polystyrene latex either by chemical crosslinking or by binding to an antibody to the IgG4 domain. The particle-bound ligands stimulated interleukin 10 secretion and inhibited interleukin 5 secretion in a mixed lymphocyte reaction using PBMCs from healthy donors.

L6 ANSWER 7 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN
2004:252539 Document No. 140:286167 Derivatives of Notch receptors ligand proteins for use as immunomodulators acting on T cells. Champion, Brian Robert; Lennard, Andrew Christopher; McKenzie, Grahame James; Tugal, Tamara (Lorantis Limited, UK). PCT Int. Appl. WO 2004024764 A1 20040325, 145 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-GB3908 20030909. PRIORITY: GB 2002-20912 20020910; GB 2002-20913 20020910; WO 2002-GB5133 20021113; WO 2002-GB5137 20021113; GB 2003-234 20030107; WO 2003-GB1525 20030404; WO 2003-GB3285 20030801.
AB Derivs. of Notch receptors ligands, such as Delta-like 1, that include the **DSL domain**, 1-5 EGF repeat domains, and the N-terminal ligand domain fused to a second peptide are described for use in modifying an immune response. A series of derivs. of the Delta-like 1 **Notch ligand** containing 2-7 EGF repeats fused a human IgG Fc domain were constructed by standard methods. The shorter deletion derivs. were able to strongly induce a Notch signaling. Jagged-1 deletion derivs. antagonizing Notch signaling are also demonstrated.

L6 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN
2004:162603 Document No. 140:210764 Modulation of immune function. Briend, Emmanuel Cyrille Pascal; Champion, Brian Robert (Lorantis Limited, UK). PCT Int. Appl. WO 2004016279 A1 20040226, 109 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-GB3556 20030813. PRIORITY: GB 2002-18879 20020814.
AB A method for modulating the immune system in a mammal is described comprising simultaneously, contemporaneously, sep. or sequentially administering: (i) an effective amount of a modulator of the Notch signaling pathway; and (ii) an effective amount of an interferon or a polynucleotide coding for an interferon.

L6 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN
2003:396917 Document No. 138:396198 **Fusion proteins** comprising human Delta or Jagged proteins as inhibitors of the Notch signalling pathway and uses in cancer therapy. Bodmer, Mark William; Briend, Emmanuel Cyrille Pascal; Champion, Brian Robert; Lennard, Andrew Christopher; McKenzie, Grahame James; Ragno, Silvia; Tugal, Tamara; Young, Lesley Lynn (Lorantis Limited, UK). PCT Int. Appl. WO 2003042246 A2 20030522, 217 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR,

KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-GB5133 20021113. PRIORITY: GB 2001-27271 20011114; GB 2002-20913 20020910.

AB The present invention provides **fusion proteins** comprising human Delta protein or Jagged protein fused with IgG as inhibitors of the Notch signalling pathway and their therapeutic uses. Specifically, the invention provides (i) a protein or polypeptide which comprises a **Notch ligand DSL domain** and 0, 1 or 2 but no more than 2 **Notch ligand** EGF-like domains; (ii) a multimer of such a protein or polypeptide (wherein each monomer may be the same or different); or (iii) a polynucleotide coding for such a protein or polypeptide; for use in the treatment of cancer. The present invention seeks to provide further methods for treating cancer and, in particular, for promoting immune responses to cancer, in particular by modification of Notch-**Notch ligand** interaction.

L6 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN

2003:396736 Document No. 138:400396 Composition comprising inhibitors of Notch signaling pathway and pathogen antigen for vaccination against infection. Bodmer, Mark William; Briend, Emmanuel Cyrille Pascal; Champion, Brian Robert; Lennard, Andrew Christopher; McKenzie, Grahame James; Ragno, Silvia; Tugal, Tamara; Young, Lesley Lynn (Lorantis Limited, UK). PCT Int. Appl. WO 2003041735 A2 20030522, 254 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-GB5137 20021113. PRIORITY: GB 2001-27267 20011114; WO 2002-GB3426 20020725; GB 2002-20849 20020907; GB 2002-20913 20020910; WO 2002-GB4390 20020927.

AB An inhibitor of the Notch signalling pathway is used in the manufacture of a medicament for use as an immunostimulant, for example as a vaccine adjuvant. The **Notch ligand** or receptor antagonists may comprise **DSL domain** of human Delta1, Delta3, or Delta4, extracellular domain of human Serrate or Jagged (Jagged 1 and 2), or EGF11 or EGF12 of human Notch1, Notch2, Notch3 or Notch4. These Notch inhibitors are capable of reducing the ability of **Notch ligand** to bind and/or activate Notch receptor on immune cells, and are capable of increasing activity of T cells, e.g. regulatory T cells, helper T cells, cytotoxic T lymphocytes, and effector T cells. The Notch signaling inhibitors are used in combination with antigen for vaccination against infection or chronic infection by pathogen such as bacteria, virus, fungus or parasite.

L6 ANSWER 11 OF 11 MEDLINE on STN

2000155994. PubMed ID: 10688816. A soluble form of human Delta-like-1 inhibits differentiation of hematopoietic progenitor cells. Han W; Ye Q; Moore M A. (Laboratory of Developmental Hematopoiesis, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA.) Blood, (2000 Mar 1) Vol. 95, No. 5, pp. 1616-25. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB Two **Notch ligand** families, Delta and Serrate/Jagged, have been identified in vertebrates. Members of the Jagged family have been shown to affect in vitro hematopoiesis. To determine whether members

of the Delta family might play a similar role in hematopoiesis, we examined the expression of mouse Delta-like-1 (mDll1). mDll1 protein was detected in whole marrow and in a marrow stromal cell line MS-5. At the RNA level, both mDll1 and Notch1 were seen in marrow precursor, differentiated hematopoietic, marrow stromal, and MS-5 cells. We isolated a cDNA encoding the human homologue of mDll1, designated human Delta-like-1 (hDll1). A soluble form of hDll1, hDll1(NDSL), containing the **DSL domain** and the N-terminal sequences, was expressed and purified from bacteria as a glutathione S-transferase (GST) **fusion protein**. We observed that hDll1(NDSL) delayed the acquisition of differentiation markers by murine hematopoietic progenitor cells (Lin-) cultured in vitro with cytokines. In addition, it promoted greater expansion (more than 3 times) of the primitive hematopoietic precursor cell population, measured in high-proliferative potential colony assay and day 12 colony-forming unit spleen (CFU-S) assay, than GST controls. We also observed that the percentage of apoptotic cells decreased and that the number of cells in the S-phase of the cell cycle increased in the cultures of Lin(-) cells with hDll1(NDSL). The effects of hDll1(NDSL) were blocked by antibody against the mouse counterpart of hDll1(NDSL), mDll1(NDSL). These observations demonstrate that hDll1 plays a role in mediating cell fate decisions during hematopoiesis. (Blood. 2000;95:1616-1625)

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=> s conjugate?
L7      513849 CONJUGATE?

=> s l7 and notch ligand
L8          10 L7 AND NOTCH LIGAND

=> dup remove l8
PROCESSING COMPLETED FOR L8
L9           10 DUP REMOVE L8 (0 DUPLICATES REMOVED)

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L9   ANSWER 1 OF 10  CAPLUS  COPYRIGHT 2007 ACS on STN
2007:259904   Document No. 146:291157  Immobilized Notch
     ligand-based system for differentiation of hematopoietic
     progenitor cells into T cells.  Roy, Krishnendu; Taqvi, Sabia (Board of
     Regents, The University of Texas System, USA).  PCT Int. Appl. WO
     2007027226 A2 20070308, 33pp.  DESIGNATED STATES: W:  AE, AG, AL, AM, AT,
     AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK,
     DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS,
     JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD,
     MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU,
     SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
     VC, VN, YU, ZA; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES,
     FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD,
     TG, TR.  (English).  CODEN: PIXXD2.  APPLICATION: WO 2006-US16228
     20060428.  PRIORITY: US 2005-675803P 20050428.
AB   The present invention generally relates to methods for the ex vivo
     expansion of undifferentiated cells.  More specifically, the present
     invention relates to systems and methods of differentiating
     undifferentiated cells into a desired lineage by providing to an
     undifferentiated cell stromal cell conditioned medium and a
     differentiation inducing ligand.  In particular, Notch
     ligand DLL4 was conjugated to biotinylated magnetic
     microbeads.  It was shown that microbeads functionalized with the
     Notch ligand DLL4 in combination with stromal cell
     paracrine factors can be used as artificial stromal cells to trigger Notch
     signaling in myoblasts and commit bone marrow hematopoietic stem cells
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(BMHSCs) to the T cell lineage in both co-culture and insert culture systems in a quant. manner. In conclusion, the authors have invented a synthetic biomaterial-based system that can effectively trigger Notch signaling during lymphocyte development from bone marrow-derived stem cells. The system of the present invention may be used to expand any undifferentiated cell that requires cell-derived soluble factors and cell-contact dependent signals. The present invention does not rely on transfected stromal cells as the signaling entity for the creation of differentiated cells.

L9 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN
2006:1280280 Document No. 146:41317 Biomaterial-based notch signaling for the differentiation of hematopoietic stem cells into T cells. Taqvi, Sabia; Dixit, Lena; Roy, Krishnendu (Department of Biomedical Engineering, University of Texas, Austin, TX, 78712, USA). Journal of Biomedical Materials Research, Part A, 79A(3), 689-697 (English) 2006. CODEN: JBMRCH. ISSN: 1549-3296. Publisher: John Wiley & Sons, Inc..
AB Thymocyte development takes place in a complex milieu of supportive cells and ECM that are responsible for the proliferation, adhesion, migration, and selection processes these cells undergo before reaching maturity. In recent years, the role of notch signaling in lymphocyte development, specifically T-cell development, was extensively characterized. Although **notch ligand** mediated signals were shown to be a necessary component of T-cell generation from stem cells, high-throughput, synthetic biomaterial-based systems for notch-directed stem-cell differentiation into lymphocytes are yet to be reported. Here, the authors present a microbead-based, artificial notch signaling system to study stem-cell differentiation into the T-cell lineage. Magnetic microbeads were functionalized with the **notch ligand** DLL4 using streptavidin-biotin binding and antibody-antigen coupling. Immunohistochem. and flow cytometry anal. indicated .apprx.65% conjugation efficiency. Efficient notch signaling through these functionalized microbeads was demonstrated through a myotube inhibition assay in C2C12 myoblasts. Thy1.2+ early T cells were successfully generated from mouse bone marrow hematopoietic stem cells (BMHSCs) using DLL4 functionalized beads using both insert-based and mixed stromal cell (OP9) coculture conditions, indicating that stem cell-stromal cell phys. contact is not necessary for DLL4 directed T-cell differentiation. Coculture studies with bead-to-cell ratios of 1:1 generated higher T-cell differentiation efficiencies, compared to bead-to-cell ratios of 5:1. These data demonstrate the promising potential of this biomaterial-based notch signaling system to generate T cells from stem cells and to elucidate the mol. interactions in T-cell development.

L9 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN
2005:120966 Document No. 142:213330 Purification of Notch receptor ligand proteins by hydrophobic interaction chromatography. Dosanjh, Bhupinder (Lorantis Limited, UK). PCT Int. Appl. WO 2005012349 A2 20050210, 66 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-GB3327 20040730. PRIORITY: WO 2003-GB3285 20030801; GB 2004-2208 20040131; GB 2004-2562 20040205.
AB Methods for purifying **Notch ligand** proteins and fragments, variants or derivs. without the use of affinity ligand peptides is described. Specifically, methods of hydrophobic interaction chromatog. (HIC) using hydrophobic derivs. of agarose and silica are used in

combination with other chromatog. methods. The purified proteins are free of endotoxins and DNA and may be suitable for therapeutic use (no data.). An N-terminal 332-amino acid fragment of human Delta-1 protein was synthesized in CHO-K1 cells. Purification of the protein by HIC on Bu Sepharose 4FF resulted in a rapid purification of the protein.

L9 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN
2005:1171811 Document No. 144:365540 Preparation of polymer matrix bioconjugated with **Notch ligand**. Konno, Tomohiro; Sakano, Seiji; Tohda, Shuji; Ito, Yoshihiro (Regenerative Med. Bioreactor Project, Kanagawa Acad. Sci. Technology, Japan). Ensho, Saisei, 25(5), 426-430 (Japanese) 2005. CODEN: ENSHCC. ISSN: 1346-8022. Publisher: Nippon Ensho-Saisei Igakkai.
AB A review. It is important to prepare the cell culture devices with functional polymer surfaces. **Notch ligand** delta-1 is considered as one of the important membrane proteins for self-renewal of hematopoietic stem cells. In this study, a polymer matrix immobilized with **Notch ligand** delta-1 was prepared by photo-immobilization technique for culture the stem cells. It has been reported that photo-reactive polymers bearing azidophenyl groups could immobilize functional proteins without losing their biol. activity. Therefore, a novel photo-reactive phospholipid polymer, 2-methacryloyloxyethyl phosphorylcholine polymer bearing azidophenyl groups, was applied as the matrix to **conjugate** with **Notch ligand** delta-1. A leukemia cell line, TMD7, was cultured on the bioconjugated polymer surface. The polymer surface immobilized with **Notch ligand** delta-1 was recognized by TMD7, and the cells efficiently grow on the phospholipid polar group concentrated surface (PC surface) with protein. It was considered that the PC surface provided a suitable environment around the membrane proteins without denaturation. The photo-reactive phospholipid polymer was expected to constitute on in vitro niche to culture hematopoietic stem cells.

L9 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN
2004:718374 Document No. 141:242022 Modulators of Notch signalling and of immune cell costimulatory activity for immunotherapy of inflammation, asthma, allergy, transplant rejection, graft versus host disease or autoimmune disease. Champion, Brian Robert; Lioumi, Maria; McKenzie, Grahame James (Lorantis Limited, UK). PCT Int. Appl. WO 2004073732 A1 20040902, 157 pp. DESIGNATED STATES: W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, ML, MR, NE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-GB668 20040218. PRIORITY: GB 2003-3663 20030218.
AB A method is described for detecting, measuring or monitoring Notch signaling by determining the amount of an immune cell costimulatory protein, polypeptide or polynucleotide or determining the amount of a polynucleotide coding for such a protein or polypeptide. The Notch signaling modulators of the invention comprise **Notch ligand** DSL domain or intracellular domain. The immune cell costimulatory proteins are CD28, CD80, CD86, CTLA-4, ICOS, ICOS ligand, CD40, CD40L, PD-1, PD-L1, PD-L2, OX40 or OX40L. Methods of modulating the immune system are also described. The Notch signaling modulators and the immune cell costimulatory activity modulators are useful for increasing or reducing

immune response against cancer or inflammation, allergy, asthma, graft vs. host disease, autoimmune disease and transplant rejection.

L9 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN
2004:633546 Document No. 141:179617 Treatment of autoimmune diseases using an activator for the notch signaling pathway. Champion, Brian Robert; Ragno, Silvia; Young, Lesley Lynn (Lorantis Limited, UK). PCT Int. Appl. WO 2004064863 A1 20040805, 244 pp. DESIGNATED STATES: W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI. (English). CODEN: PIXXD2. APPLICATION: WO 2004-GB263 20040123. PRIORITY: GB 2003-1519 20030123; GB 2003-1518 20030123; GB 2003-1515 20030123; GB 2003-1513 20030123; GB 2003-1512 20030123; GB 2003-1510 20030123; GB 2003-1521 20030123; GB 2003-1522 20030123; GB 2003-1524 20030123; GB 2003-1526 20030123; GB 2003-1527 20030123; GB 2003-1529 20030123; WO 2003-GB1525 20030404; GB 2003-12062 20030524; WO 2003-GB3285 20030801; GB 2003-23130 20031003; WO 2004-GB46 20040107.
AB A product is disclosed comprising a modulator of the Notch signaling pathway; and an autoantigen or bystander antigen, or a polynucleotide coding for an autoantigen or bystander antigen; as a combined preparation for simultaneous, contemporaneous, sep. or sequential use for modulation of immune response. The invention relates to modulators of notch signalling pathway for T cell activation, and therapeutic use in immunosuppression. In the examples of the invention, a fusion protein comprising the extracellular domain of human Delta1 ligand fused to the Fc domain of human IgG4.

L9 ANSWER 7 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN
2004:589350 Document No. 141:145678 Particle-bound modulators of the Notch signaling pathway for use in the treatment of disorders of the immune system. Bodmer, Mark William; Briend, Emmanuel Cyrille Pascal; Champion, Brian Robert; Lennard, Andrew Christopher; McKenzie, Grahame James; Tugal, Tamara; Ward, George Albert; Young, Lesley Lynn (Lorantis Limited, UK). PCT Int. Appl. WO 2004060262 A2 20040722, 294 pp. DESIGNATED STATES: W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GH, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ. (English). CODEN: PIXXD2. APPLICATION: WO 2004-GB46 20040107. PRIORITY: GB 2003-234 20030107; GB 2003-1519 20030123; GB 2003-1510 20030123; GB 2003-1512 20030123; GB 2003-1522 20030123; GB 2003-1524 20030123; GB 2003-1521 20030123; GB 2003-1518 20030123; GB 2003-1515 20030123; GB 2003-1513 20030123; GB 2003-1529 20030123; GB 2003-1526 20030123; GB 2003-1527 20030123; GB 2003-6621 20030322; WO 2003-GB1525 20030404; GB 2003-12062 20030524; WO 2003-GB3285 20030801; GB 2003-23130 20031003.
AB Modulators of Notch signaling are immobilized on pharmaceutically acceptable carriers for therapeutic use in the treatment of immune disorders. Two derivs. of the **Notch ligand** Delta were prepared: a fusion protein with IgG4 and a cysteine-rich derivative These were immobilized on Dynabeads or polystyrene latex either by chemical crosslinking or by binding to an antibody to the IgG4 domain. The particle-bound ligands stimulated interleukin 10 secretion and inhibited interleukin 5 secretion in a mixed lymphocyte reaction using PBMCs from healthy donors.

L9 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN
2004:252539 Document No. 140:286167 Derivatives of Notch receptors ligand

proteins for use as immunomodulators acting on T cells. Champion, Brian Robert; Lennard, Andrew Christopher; McKenzie, Grahame James; Tugal, Tamara (Lorantis Limited, UK). PCT Int. Appl. WO 2004024764 A1 20040325, 145 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-GB3908 20030909. PRIORITY: GB 2002-20912 20020910; GB 2002-20913 20020910; WO 2002-GB5133 20021113; WO 2002-GB5137 20021113; GB 2003-234 20030107; WO 2003-GB1525 20030404; WO 2003-GB3285 20030801.

AB Derivs. of Notch receptors ligands, such as Delta-like 1, that include the DSL domain, 1-5 EGF repeat domains, and the N-terminal ligand domain fused to a second peptide are described for use in modifying an immune response. A series of derivs. of the Delta-like 1 **Notch ligand** containing 2-7 EGF repeats fused a human IgG Fc domain were constructed by standard methods. The shorter deletion derivs. were able to strongly induce a Notch signaling. Jagged-1 deletion derivs. antagonizing Notch signaling are also demonstrated.

L9 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN

2003:837139 Document No. 139:336935 Particle-bound Notch pathway-modifying immunomodulators for immunotherapy of cancer, allergy, infection, inflammation, and autoimmune disease and for modulator screening. Bodmer, Mark William; Briend, Emmanuel Cyrille Pascal; Champion, Brian Robert; Lennard, Andrew Christopher; McKenzie, Grahame James; Tugal, Tamara; Ward, George Albert; Young, Lesley Lynn (Lorantis Limited, UK). PCT Int. Appl. WO 2003087159 A2 20031023, 177 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-GB1525 20030404. PRIORITY: GB 2002-7930 20020405; GB 2002-7929 20020405; GB 2002-12282 20020528; GB 2002-12283 20020528; WO 2002-GB3397 20020725; WO 2002-GB3426 20020725; GB 2002-20913 20020910; GB 2002-20912 20020910; GB 2003-234 20030107.

AB A method is disclosed for therapeutic modulation of Notch signalling by administering modulators of the Notch signal transduction pathway bound to a pharmaceutically acceptable carrier. The modulators may be in mixts. of up to 100 different entities. The modulators may also be **conjugated** with one another, e.g. in fusion proteins. The construction of a CHO-derived cell line carrying a Notch pathway-dependent luciferase reporter gene to screen for **Notch ligands** is described.

L9 ANSWER 10 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN

2003:118018 Document No. 138:168835 Targeting of an antigen presenting cell (APC) with a modulator of T cell signalling, such as a **Notch ligand**, coupled to the MHC class II-binding motif from a superantigen. Bodmer, Mark William; Champion, Brian Robert; McKenzie, Grahame James; Nye, Lucy Emma (Lorantis Limited, UK). PCT Int. Appl. WO 2003012111 A2 20030213, 93 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN,

TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-GB3381 20020725. PRIORITY: GB 2001-18155 20010725.

AB The present invention relates to the concept of delivering a modulator of T cell signaling, such as a **Notch ligand**, to an antigen presenting cell (APC). The targeting approach disclosed uses, for example, the major histocompatibility complex (MHC) class II binding motif from a superantigen coupled to a modulator of the Notch signaling pathway. Superantigens bind both MHC class II mols. and subsets of T cell receptors and thus effectively cross-link APCs to T cells and activate cells polyclonally. The mol. regions of these mols. that impart T cell receptor (TCR) and MHC class II binding have been defined structurally and have been shown to be distinct regions of the mol. By using the MHC class II binding domain with a modulator of the Notch signaling pathway we can focus the activity of the Notch signaling pathway modulator to the APCs at the site of delivery. Further, the domain lacks toxin activity because it cannot find the T cell receptor to activate T cells. According to one aspect of the present invention there is provided a **conjugate** comprising a first and a second sequence wherein the first sequence comprises a polypeptide which is capable of binding to an APC, or a polynucleotide encoding therefor, and the second sequence comprises a polypeptide comprising a modulator of a signaling pathway in a T cell or a polynucleotide encoding therefor.

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L10 ANSWER 1 OF 44 CAPLUS COPYRIGHT 2007 ACS on STN
2006:945773 Document No. 145:331234 Notch signaling-directed neural differentiation of mammalian embryonic stem cells. Lowell, Sarah, Elizabeth; Smith, Austin, Gerard; Heavey, Barry (The University Court of the University of Edingburgh, UK). PCT Int. Appl. WO 2006095175 A1 20060914, 119pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2006-GB836 20060309. PRIORITY: GB 2005-4881 20050309.

AB Differentiation towards a neural fate, and away from a non-neural fate, is promoted by activation of Notch signaling in embryonic stem (ES) cells and then transferring the cells into neural differentiation protocols. Media for neural differentiation comprises a Notch activator, e.g., a **Notch ligand** that can be clustered. Genetic manipulation is used as an alternative to media additives for Notch activation. A **fusion protein** of an activated form of a Notch receptor and a transduction domain, and a **fusion protein** of a downstream effector of Notch signaling and a transduction domain are provided.

L10 ANSWER 2 OF 44 CAPLUS COPYRIGHT 2007 ACS on STN
2006:950172 Document No. 145:328369 Treatment of allergy using a modulator of the Notch signaling pathway along with an allergen. Bodmer, Mark William; Briend, Emmanuel Cyrille Pascal; Champion, Brian Robert; Lennard,

Andrew Christopher; McKenzie, Grahame James; Ragno, Silvia; Tugal, Tamara; Ward, George Albert; Young, Lesley Lynn (UK). U.S. Pat. Appl. Publ. US 2006205823 A1 20060914, 103pp., Cont.-in-part of Appl. No. PCT/GB04/001252. (English). CODEN: USXXCO. APPLICATION: US 2005-231494 20050921. PRIORITY: GB 2003-6583 20030321; GB 2003-6582 20030321; GB 2003-6650 20030322; GB 2003-6651 20030322; GB 2003-6654 20030322; GB 2003-6621 20030322; GB 2003-6622 20030322; GB 2003-6626 20030322; GB 2003-6624 20030322; GB 2003-6640 20030322; GB 2003-6644 20030322; WO 2003-GB1525 20030404; GB 2003-12062 20030524; WO 2003-GB3285 20030801; GB 2003-23130 20031003; WO 2004-GB46 20040107; WO 2004-GB263 20040123; WO 2004-GB1252 20040322.

AB The invention provides a method for reducing an immune response to an allergen or antigenic determinant thereof in a mammal by administering a modulator of the Notch signalling pathway. The invention provides a product comprising a modulator of the Notch signalling pathway and an allergen or a polynucleotide coding for an allergen, as a combined preparation for simultaneous, contemporaneous, sep. or sequential use for promoting immune tolerance. The modulators of the Notch signalling pathway comprises **Notch ligands**, such as Delta or Jagged, and DSL, EGF-like or extracellular domains thereof. Sequences of Delta-1/Ig-Fc **fusion proteins** are provided. Notch signaling pathway modulation was demonstrated on mouse model.

L10 ANSWER 3 OF 44 CAPLUS COPYRIGHT 2007 ACS on STN

2006:632269 Document No. 145:81950 Exposing isolated donor antigen-presenting cells to modulators of Notch signalling to treat GVHD and transplant-associated conditions. Champion, Brian Robert; Solari, Roberto Celeste Ercole; Dallman, Margaret Jane; Lamb, Jonathan Robert; Hoyne, Gerard Francis; Briend, Emmanuel Cyrille Pascal (UK). U.S. Pat. Appl. Publ. US 2006140943 A1 20060629, 77 pp., Cont.-in-part of Appl. No. PCT/GB03/03874. (English). CODEN: USXXCO. APPLICATION: US 2005-71796 20050303. PRIORITY: GB 2002-20658 20020905; WO 2003-GB3874 20030905.

AB There is provided a use of a modulator of Notch signaling for the preparation of a medicament for treatment of Graft Vs. Host Disease (GVHD) and diseases and conditions caused by or associated with transplants such as organ, tissue and/or cell transplants (e.g. bone marrow transplants), wherein the modulator is used to reduce the reactivity of cells of the immune system. The modulator is a **Notch ligand** or a fragment or analog, or is selected from the group consisting of an organic compound, inorg. compound, peptide, polypeptide, polynucleotide, antibody, or antibody fragment. The modulator is derived from Delta or Serrate family of proteins, or polynucleotide sequence encoding therefore. Antigen-presenting cells are e.g. T cells or dendritic cells.

L10 ANSWER 4 OF 44 CAPLUS COPYRIGHT 2007 ACS on STN

2006:559208 Document No. 145:61476 Modulators of Notch signaling and cytokine expression for immunotherapy of inflammation and autoimmune disease. Champion, Brian Robert; Young, Lesley Lynn; Mckenzie, Grahame James (UK). U.S. Pat. Appl. Publ. US 2006128619 A1 20060615, 92 pp. (English). CODEN: USXXCO. APPLICATION: US 2005-178724 20050711. PRIORITY: GB 2003-428 20030109; WO 2004-GB21 20040109.

AB The invention provides a method for modifying IL-4 expression in a cell using a modulator of Notch signaling. It also provides methods for generating immune modulatory cytokine profiles with increased IL-4 expression and/or increased IL-10 expression and/or reduced IL-5, IL-13 and TNFα expression. In addition, the invention provides a method for increasing a TH2 immune response and/or decreasing a TH1 immune response in a cell, using a modulator of Notch signaling. The modulators of Notch signaling comprise Notch receptor agonists or antagonists, particularly **fusion proteins** comprising DSL or EGF domains from Delta or Jagged proteins and an Ig Fc segment. Alternatively, the modulator of Notch signaling comprises a Notch intracellular domain. The invention

also claims polynucleotides encoding modulators of Notch signaling. Methods of the invention are claimed for use in treating inflammation or an autoimmune condition. In the examples, modulation of cytokine production in mouse and human CD4+ cells by soluble or immobilized human Delta 1 extracellular domain-IgG4Fc **fusion protein** was measured. Expression of IL-10, IFN-γ, and transcription factors Tbet, c-Maf, and GATA-3 was measured in anti-CD3/28 activated mouse T cells under neutral, TH1, or TH2 culture conditions after treatment with the Delta1-Fc protein.

L10 ANSWER 5 OF 44 CAPLUS COPYRIGHT 2007 ACS on STN
2006:941040 Document No. 145:328348 Tumor immunotherapy using IgG Fc fragment fused with **notch ligand** delta or shRNA targeting jagged. Asutomo, Koji (Tokushima University, Japan). Jpn. Kokai Tokkyo Koho JP 2006241087 A 20060914, 15pp. (Japanese). CODEN: JKXXAF. APPLICATION: JP 2005-59885 20050304.
AB Described is an immunotherapy agent for treating tumor, which comprises IgG Fc fragment fused with **notch ligand** delta or shRNA targeting jagged. The **fusion protein** enhances the expression of delta 1 or delta 4, but the shRNA inhibits the expression of jagged 1 or jagged 2. The protein sequences of delta 1 or delta 4 from human and mouse are also provided. ShRNAs targeting human and mouse jagged 1 or jagged 2 are further provided. The **fusion protein** of Delta1-IgG Fc more effectively decreased the size of tumor in the mouse model transplanted with 3T1 cells as compared to the treatment with IgG alone. DC-Delta1 (Dendritic cell transformant with over-expressed Delta1), DC-Delta1/Jagged1low (Dendritic cell transformant with over-expressed Delta1 and under-expressed Jagged 1) , and DC-Delta1/Jagged2low (Dendritic cell transformant with over-expressed Delta1 and under-expressed Jagged 2) significantly decreased the tumor size in the mouse model compared to the control treated with DC clone. DC-Delta4 (Dendritic cell transformant with over-expressed Delta4), DC-Delta4/Jagged1low, and DC-Delta4/Jagged2low also significantly decreased the tumor size in the mouse model compared to the control treated with DC clone.

L10 ANSWER 6 OF 44 CAPLUS COPYRIGHT 2007 ACS on STN
2005:387813 Document No. 142:446015 **Notch ligands** by Delta 1 or Serrate 1 reducing peripheral immune responses for therapeutic uses. Lamb, Jonathan Robert; Dallman, Margaret Jane; Hoyne, Gerard Francis (Lorantis Limited, UK). U.S. US 6887475 B1 20050503, 95 pp., Cont.-in-part of Appl. No. PCT/GB97/03058. (English). CODEN: USXXAM. APPLICATION: US 1999-310685 19990504. PRIORITY: GB 1996-23236 19961107; GB 1997-15674 19970724; GB 1997-19350 19970911; WO 1997-GB3058 19971106.
AB The present invention relates to the use of therapeutic compds. in the modification of T-cells, T-cell-antigen presenting cell (APC) interactions and the interaction between pathogenic organism and immunocompetent cells of a host. In particular, it relates to the use of these compds. in the modulation of the interaction between Notch proteins and their ligands and to the use of such compds. in the therapy of conditions such as graft rejection, autoimmunity, allergy, asthma and infectious diseases.

L10 ANSWER 7 OF 44 MEDLINE on STN
2005235738. PubMed ID: 15870272. Negative feedback regulation of Met-dependent invasive growth by Notch. Stella M Cristina; Trusolino Livio; Pennacchietti Selma; Comoglio Paolo M. (Institute for Cancer Research and Treatment, University of Turin School of Medicine, Division of Molecular Oncology, IV Floor, Str. Prov. 142, Km. 3,95, 10060 Candiolo, Torino, Italy.. mariacristina.stella@ircc.it) . Molecular and cellular biology, (2005 May) Vol. 25, No. 10, pp. 3982-96. Journal code: 8109087. ISSN: 0270-7306. Pub. country: United States. Language: English.
AB The hepatocyte growth factor (HGF) receptor encoded by the Met oncogene

controls a genetic program-known as "invasive growth"-responsible for several developmental processes and involved in cancer invasion and metastasis. This program functions through several regulatory gene products, as yet largely unknown, both upstream and downstream of Met. Here we show that activation of the Notch receptor results in transcriptional down-regulation of Met, suppression of HGF-dependent Ras signaling, and impairment of HGF-dependent cellular responses. In turn, Met activation leads to transcriptional induction of the **Notch ligand** Delta and the Notch effector HES-1, indicating that Met is able to self-tune its own protein levels and the ensuing biochemical and biological outputs through stimulation of the Notch pathway. By using branching morphogenesis of the tracheal system in Drosophila as a readout of invasive growth, we also show that exogenous expression of a constitutively active form of human Met induces enhanced sprouting of the tracheal tree, a phenotype that is further increased in embryos lacking Notch function. These results unravel an in-built mechanism of negative feedback regulation in which Met activation leads to transcriptional induction of Notch function, which in turn limits HGF activity through repression of the Met oncogene.

L10 ANSWER 8 OF 44 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
2006:183399 Document No.: PREV200600185511. Delta-1 promotes soluble IL-6R-Mediated action of IL-6 on human erythropoiesis while counteracting the effect of IL-6 on the generation of myeloid-lineage cells. Yamamura, Kentaro [Reprint Author]; Ohishi, Kohshi; Katayama, Naoyuki; Shiku, Hiroshi; Nishikawa, Mitsuo; Nakahata, Tatsutoshi. Mie Univ, Dept Hematol and Oncol, Grad Sch Med, Tsu, Mie 514, Japan. Blood, (NOV 16 2005) Vol. 106, No. 11, Part 1, pp. 879A.
Meeting Info.: 47th Annual Meeting of the American-Society-of-Hematology. Atlanta, GA, USA. December 10 -13, 2005. Amer Soc Hematol.
CODEN: BLOOAW. ISSN: 0006-4971. Language: English.

AB **Notch ligand** Delta-1 is shown to influence proliferation and differentiation of hematopoietic progenitors by interacting with various cytokines. IL-6 exerts various effects on human hematopoiesis by activating gp130 via soluble IL-6 receptor (R) as well as membrane-bound IL-6R. However, little is known about the interaction between Deltal and gp130 activation in human hematopoiesis. We previously reported that Delta-1 in combination with IL-6R/IL-6 **fusion protein** FP6, which directly and agonistically activates gp130, enhances the production of mixed and pure erythroid progenitors from cord blood CD34(+)CD38(-) cells, while not significantly affecting the generation of myeloid progenitors (ASH 2004). Here, we examined the interaction between Delta-1 and gp130 activation in the generation of erythroid cells and myeloid-lineage cells from cord blood CD34'CD38cells in serum-free suspension cultures. In the presence of SCF, Flt3L, TPO, and IL-3 (4GF), Delta-1 acted synergistically with FP6 to promote the production of CD36(+)glycophorin A (GPA)(high) erythroid cells from CD34(+)CD38(-) cells. whereas few CD36(+)GPA(high) erythroid cells were generated by Delta-1, IL-6, and Delta-1 plus IL-6. When we assessed the stage of erythroid cells affected by Defta-1 and FP6, Delta-1, in conjunction with FP6, augmented the generation of CD36(+)GPA(high) erythroid cells from CD34(+)CD38(-) cell-derived CD36(+)GPA(-) erythroid progenitors equivalent to BFU-E stage but not from CD34(+)CD38(-)cell-derived CD36(+)GPA(low) erythroid progenitors equivalent to CFU-E stage. Oil the other hand, IL-6 and FP6 increased the production of CD 14(+) monocytic cells and CD15(+) granulocytic cells from CD34+CD38- cells. Delta-1 had opposite effect and antagonized the stimulatory effect of IL-6 and FP6 on the generation of monocytic and granulocytic cells. Although the development of CD1a(+)CD14(-) dendritic cells from CD34(+)CD38(-) cells was suppressed by IL6 and FP-6 but instead potentiated by Delta-1, Delta-1 competed with the inhibitory effect of IL-6 and FP6 on the generation of dendritic cells. These data indicate that Delta-1 modulates

the effect of IL-6 on human hematopoiesis by enhancing its soluble IL-6R-mediated action on early erythropoiesis while antagonizing its effect on the generation of myeloid-lineage cells.

L10 ANSWER 9 OF 44 MEDLINE on STN
2005468280. PubMed ID: 16075259. [Significance of molecular-cytogenetic findings in mucoepidermoid carcinoma as an example of salivary gland tumors]. Bedeutung molekular-zytogenetischer Befunde bei Speicheldrusentumoren am Beispiel des Mukoepidermoidkarzinoms. Roser K; Jakel K T; Bullerdiek J; Loning T. (Speicheldrusenregister, Institut fur Oralpathologie, Universitatsklinikum Hamburg-Eppendorf.) Der Pathologe, (2005 Sep) Vol. 26, No. 5, pp. 359-66. Ref: 27. Journal code: 8006541. ISSN: 0172-8113. Pub. country: Germany: Germany, Federal Republic of. Language: German.
AB Chromosome translocations in tumors frequently give rise to fusion genes encoding proteins with oncogenic activities. Mucoepidermoid carcinomas (MEC) are characterized by a t(11;19)(q21-22;p13) translocation found in approximately 60% of the tumors. This t(11;19) translocation results in a fusion gene consisting of exon 1 of the MECT 1 gene and exons 2-5 of the MAML 2 gene. As a result of the t(11;19) a **fusion protein** is generated which, independent of **NOTCH-ligands**, activates the transcription of the NOTCH target gene HES 1. The altered function of MAML 2 causes a disruption of NOTCH signalling which suggests a novel mechanism of tumorigenesis. Pending the elucidation of the t(11;19) at the molecular level of an apparently identical chromosomal translocation in Warthin's tumor, the identification of the translocation in MEC by FISH- and/or RT-PCR-analyses may become important in diagnosis and might have prognostic relevance. Warthin's tumors are benign salivary gland neoplasms with a distinctive histomorphology and histogenesis completely different from MEC.

L10 ANSWER 10 OF 44 CAPLUS COPYRIGHT 2007 ACS on STN
2004:857429 Document No. 141:325713 Notch signalling modulation using a KLF and its effectors, diagnostic assays and therapeutics for autoimmune and inflammatory disorders. Champion, Brian Robert; Lioumi, Maria; McKenzie, Grahame James; Young, Lesley Lynn (Lorantis Limited, UK). PCT Int. Appl. WO 2004087195 A2 20041014, 150 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-GB1379 20040329. PRIORITY: GB 2003-7472 20030401.
AB A method is described for detecting, measuring or monitoring Notch signalling by determining the amount of a KLF (Kruppel-like factor) protein, or determining the amount of a polynucleotide coding for KLF. Methods of modulating the immune system by modulation of KLF activity and methods of modulating immune cell quiescence and proliferation are also described. A preferred KLF is human KLF-2, also known as LKLF (Q9Y5W3, NM_016270). Modulators of the Notch signalling pathway also comprise **Notch ligands**, such as Delta or Jagged, and DSL, EGF-like or extracellular domains thereof and polynucleotides coding for such proteins. Sequences of Delta-1/Ig-Fc **fusion proteins** are provided. Notch signaling pathway modulation was demonstrated in mouse model.

L10 ANSWER 11 OF 44 CAPLUS COPYRIGHT 2007 ACS on STN
2004:799474 Document No. 141:289039 Treatment of allergy using a modulator of the Notch signaling pathway along with an allergen. Bodmer, Mark

William; Briend, Emmanuel Cyrille Pascal; Champion, Brian Robert; Lennard, Andrew Christopher; McKenzie, Grahame James; Ragno, Silvia; Tugal, Tamara; Ward, George Albert; Young, Lesley Lynn (Lorantis Limited, UK). PCT Int. Appl. WO 2004082710 A1 20040930, 176 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-GB1252 20040322. PRIORITY: GB 2003-6583 20030321; GB 2003-6582 20030321; GB 2003-6621 20030322; GB 2003-6622 20030322; GB 2003-6626 20030322; GB 2003-6624 20030322; GB 2003-6640 20030322; GB 2003-6644 20030322; GB 2003-6650 20030322; GB 2003-6651 20030322; GB 2003-6654 20030322; WO 2003-GB1525 20030404; GB 2003-12062 20030524; WO 2003-GB3285 20030801; GB 2003-23130 20031003; WO 2004-GB46 20040107; WO 2004-GB263 20040123.

AB The invention provides a method for reducing an immune response to an allergen or antigenic determinant thereof in a mammal by administering a modulator of the Notch signalling pathway. The invention provides a product comprising a modulator of the Notch signalling pathway and an allergen or a polynucleotide coding for an allergen, as a combined preparation for simultaneous, contemporaneous, sep. or sequential use for promoting immune tolerance. The modulators of the Notch signalling pathway comprises **Notch ligands**, such as Delta or Jagged, and DSL, EGF-like or extracellular domains thereof. Sequences of Delta-1/Ig-Fc **fusion proteins** are provided. Notch signaling pathway modulation was demonstrated on mouse model.

L10 ANSWER 12 OF 44 CAPLUS COPYRIGHT 2007 ACS on STN

2004:718374 Document No. 141:242022 Modulators of Notch signalling and of immune cell costimulatory activity for immunotherapy of inflammation, asthma, allergy, transplant rejection, graft versus host disease or autoimmune disease. Champion, Brian Robert; Lioumi, Maria; McKenzie, Grahame James (Lorantis Limited, UK). PCT Int. Appl. WO 2004073732 A1 20040902, 157 pp. DESIGNATED STATES: W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, ML, MR, NE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-GB668 20040218. PRIORITY: GB 2003-3663 20030218.

AB A method is described for detecting, measuring or monitoring Notch signaling by determining the amount of an immune cell costimulatory protein, polypeptide or polynucleotide or determining the amount of a polynucleotide coding for such a protein or polypeptide. The Notch signaling modulators of the invention comprise **Notch ligand** DSL domain or intracellular domain. The immune cell costimulatory proteins are CD28, CD80, CD86, CTLA-4, ICOS, ICOS ligand, CD40, CD40L, PD-1, PD-L1, PD-L2, OX40 or OX40L. Methods of modulating the immune system are also described. The Notch signaling modulators and the immune cell costimulatory activity modulators are useful for increasing or reducing immune response against cancer or inflammation, allergy, asthma, graft vs. host disease, autoimmune disease and transplant rejection.

L10 ANSWER 13 OF 44 CAPLUS COPYRIGHT 2007 ACS on STN

2004:633546 Document No. 141:179617 Treatment of autoimmune diseases using an activator for the notch signaling pathway. Champion, Brian Robert; Ragno, Silvia; Young, Lesley Lynn (Lorantis Limited, UK). PCT Int. Appl. WO 2004064863 A1 20040805, 244 pp. DESIGNATED STATES: W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI. (English). CODEN: PIXXD2. APPLICATION: WO 2004-GB263 20040123. PRIORITY: GB 2003-1519 20030123; GB 2003-1518 20030123; GB 2003-1515 20030123; GB 2003-1513 20030123; GB 2003-1512 20030123; GB 2003-1510 20030123; GB 2003-1521 20030123; GB 2003-1522 20030123; GB 2003-1524 20030123; GB 2003-1526 20030123; GB 2003-1527 20030123; GB 2003-1529 20030123; WO 2003-GB1525 20030404; GB 2003-12062 20030524; WO 2003-GB3285 20030801; GB 2003-23130 20031003; WO 2004-GB46 20040107.

AB A product is disclosed comprising a modulator of the Notch signaling pathway; and an autoantigen or bystander antigen, or a polynucleotide coding for an autoantigen or bystander antigen; as a combined preparation for simultaneous, contemporaneous, sep. or sequential use for modulation of immune response. The invention relates to modulators of notch signalling pathway for T cell activation, and therapeutic use in immunosuppression. In the examples of the invention, a **fusion protein** comprising the extracellular domain of human Delta1 ligand fused to the Fc domain of human IgG4.

L10 ANSWER 14 OF 44 CAPLUS COPYRIGHT 2007 ACS on STN

2004:610096 Document No. 141:156082 Methods for use of Notch signaling for modulation of cytokine production in T cells and therapeutic uses thereof. Champion, Brian Robert; Young, Lesley Lynn; McKenzie, Grahame James (Lorantis Limited, UK). PCT Int. Appl. WO 2004062686 A2 20040729, 149 pp. DESIGNATED STATES: W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GH, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ. (English). CODEN: PIXXD2. APPLICATION: WO 2004-GB21 20040109. PRIORITY: GB 2003-428 20030109.

AB The invention provides methods for use of modulators of Notch signaling to regulate interleukin 4 expression and T cell immune responses. The invention further claims use of the methods for immunotherapy, to modify the TH1/TH2 balance of an immune response in favor of a TH2 response, by treatment of patient's cells in vivo or ex vivo. In the examples of the invention, a **fusion protein** comprising the extracellular domain of human Delta1 ligand fused to the Fc domain of human IgG4 was immobilized in microtiter plates via its Fc domain. CD4-pos. cell were cultured in the presence of the above **fusion protein**, stimulated with anti-CD28 antibody, and analyzed for cDNA expression by PCR. The CD4+ cells were restimulated in various ways and the cytokines IL-10 and interferon-γ were measured. **Notch ligand** signaling was also measured using a luciferase reporter construct in CHO cells cocultured with recombinant CHO cells expressing Delta1 ligand on the surface. Cytokine production was measured in stimulated mouse CD4+ cells under polarizing conditions. Transcription factor and cytokine expression by anti-CD3/28 activated mouse T cells activated under neutral, Th1, or Th2 culture conditions was measured with or without Delta1 protein.

L10 ANSWER 15 OF 44 CAPLUS COPYRIGHT 2007 ACS on STN

2004:589350 Document No. 141:145678 Particle-bound modulators of the Notch

signaling pathway for use in the treatment of disorders of the immune system. Bodmer, Mark William; Briend, Emmanuel Cyrille Pascal; Champion, Brian Robert; Lennard, Andrew Christopher; McKenzie, Grahame James; Tugal, Tamara; Ward, George Albert; Young, Lesley Lynn (Lorantis Limited, UK). PCT Int. Appl. WO 2004060262 A2 20040722, 294 pp. DESIGNATED STATES: W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GH, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ. (English). CODEN: PIXXD2. APPLICATION: WO 2004-GB46 20040107. PRIORITY: GB 2003-234 20030107; GB 2003-1519 20030123; GB 2003-1510 20030123; GB 2003-1512 20030123; GB 2003-1522 20030123; GB 2003-1524 20030123; GB 2003-1521 20030123; GB 2003-1518 20030123; GB 2003-1515 20030123; GB 2003-1513 20030123; GB 2003-1529 20030123; GB 2003-1526 20030123; GB 2003-1527 20030123; GB 2003-6621 20030322; WO 2003-GB1525 20030404; GB 2003-12062 20030524; WO 2003-GB3285 20030801; GB 2003-23130 20031003.

AB Modulators of Notch signaling are immobilized on pharmaceutically acceptable carriers for therapeutic use in the treatment of immune disorders. Two derivs. of the **Notch ligand** Delta were prepared: a **fusion protein** with IgG4 and a cysteine-rich derivative These were immobilized on Dynabeads or polystyrene latex either by chemical crosslinking or by binding to an antibody to the IgG4 domain. The particle-bound ligands stimulated interleukin 10 secretion and inhibited interleukin 5 secretion in a mixed lymphocyte reaction using PBMCs from healthy donors.

L10 ANSWER 16 OF 44 CAPLUS COPYRIGHT 2007 ACS on STN

2004:252539 Document No. 140:286167 Derivatives of Notch receptors ligand proteins for use as immunomodulators acting on T cells. Champion, Brian Robert; Lennard, Andrew Christopher; McKenzie, Grahame James; Tugal, Tamara (Lorantis Limited, UK). PCT Int. Appl. WO 2004024764 A1 20040325, 145 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-GB3908 20030909. PRIORITY: GB 2002-20912 20020910; GB 2002-20913 20020910; WO 2002-GB5133 20021113; WO 2002-GB5137 20021113; GB 2003-234 20030107; WO 2003-GB1525 20030404; WO 2003-GB3285 20030801.

AB Derivs. of Notch receptors ligands, such as Delta-like 1, that include the DSL domain, 1-5 EGF repeat domains, and the N-terminal ligand domain fused to a second peptide are described for use in modifying an immune response. A series of derivs. of the Delta-like 1 **Notch ligand** containing 2-7 EGF repeats fused a human IgG Fc domain were constructed by standard methods. The shorter deletion derivs. were able to strongly induce a Notch signaling. Jagged-1 deletion derivs. antagonizing Notch signaling are also demonstrated.

L10 ANSWER 17 OF 44 CAPLUS COPYRIGHT 2007 ACS on STN

2004:162603 Document No. 140:210764 Modulation of immune function. Briend, Emmanuel Cyrille Pascal; Champion, Brian Robert (Lorantis Limited, UK). PCT Int. Appl. WO 2004016279 A1 20040226, 109 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU,

ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-GB3556 20030813. PRIORITY: GB 2002-18879 20020814.

AB A method for modulating the immune system in a mammal is described comprising simultaneously, contemporaneously, sep. or sequentially administering: (i) an effective amount of a modulator of the Notch signaling pathway; and (ii) an effective amount of an interferon or a polynucleotide coding for an interferon.

L10 ANSWER 18 OF 44 MEDLINE on STN

2004558164. PubMed ID: 15531953. Axoglial interaction via the notch receptor in oligodendrocyte differentiation. Hu Q D; Cui X Y; Ng Y K; Xiao Z C. (Department of Clinical Research, Singapore General Hospital, Singapore.) Annals of the Academy of Medicine, Singapore, (2004 Sep) Vol. 33, No. 5, pp. 581-8. Ref: 84. Journal code: 7503289. ISSN: 0304-4602. Pub. country: Singapore. Language: English.

AB INTRODUCTION: Increasing evidence has revealed that the Notch signalling pathway is one of the pivotal systems that mediate oligodendrocyte development. The Notch receptor is a type I transmembrane molecule that represents a novel cellular signalling paradigm, namely, regulated intramembrane proteolysis (RIP). METHOD: The typical **Notch ligands**, such as Delta, Serrate/Jagged and Lag2 (DSL), promote the formation of oligodendocyte precursor cells (OPCs) and maintain them in an uncommitted stage, thus retarding oligodendrocyte appearance in the central nervous system (CNS). RESULTS: In contrast, our recent studies have revealed that F3/contactin, a GPI-linked neural adhesion molecule, interacts with Notch and speeds up the generation and maturation of oligodendrocytes. CONCLUSIONS: Considering the distinct, albeit somewhat overlapping expression patterns of F3 and DSL in the CNS, the Notch receptor appears to function ligand-dependently during oligodendrocyte development. This multipotentiality may well designate the Notch receptor as one of the therapeutic targets that one can manoeuvre to treat demyelinating diseases, such as multiple sclerosis, that is characterised by chronic myelin degeneration.

L10 ANSWER 19 OF 44 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

2005:477694 Document No.: PREV200510269598. Synergistic interaction between **Notch ligand** Delta-1 and IL-6/soluble IL-6 receptor **fusion protein** in the generation of BFU-E from primitive hematopoietic progenitors. Yamamura, Kentaro [Reprint Author]; Ohishi, Kohshi; Katayama, Naoyuki; Shiku, Hiroshi; Masuya, Masahiro; Heike, Yuji; Nishikawa, Mitsuo; Nakahata, Tatsutoshi. Mie Univ, Sch Med, Dept Internal Med 2, Tsu, Mie 514, Japan. Blood, (NOV 16 2004) Vol. 104, No. 11, Part 1, pp. 452A.
Meeting Info.: 46th Annual Meeting of the American-Society-of-Hematology. San Diego, CA, USA. December 04 -07, 2004. Amer Soc Hematol.
CODEN: BLOOAW. ISSN: 0006-4971. Language: English.

AB We have previously reported that **Notch ligand** Delta-1 may enhance the generation of NOD/SCID-repopulating hematopoietic stem cells and thymus-repopulating Tcell precursors from cord blood [CB] CD34+CD38- cells. A complex of IL-6/soluble IL-6 receptor is shown to induce the expansion and proliferation of primitive hematopoietic progenitors that express gp130 but not the IL-6 receptor alpha chain, in mobilized peripheral blood (MPB) as well as in CB. In this study,we explored the interaction between Delta-1 and IL-6/soluble IL-6 receptor **fusion protein** [FP] in the generation of hematopoietic progenitors from MPB- andCB-derived primitive hematopoietic progenitors. MPB qCD34+Thy-1+ cells were cultured in serum-free medium with SCF, flt-3 ligand, TPO, and IL-3 [4GF), 4GF plus Delta-1, 4GF plus FP, and 4GF plus FP plus Delta-1. Delta-1 was used after immobilized to the culture

plates. Freshly isolated cells and cultured cellswere assessed for colony-forming ability by replating cells into semisolid medium containing SCF, flt-3 ligand, TPO, IL-3, IL-6, G-CSF, GM-CSF, and EPO. Colonies were counted at day 14. The numbers of BFU-E, CFU-Mix, and CFU-GM were 37-fold, 18-fold, and 135-fold increased, respectively, in cultures with 4GF plus FP, as compared with those in freshly isolated cells. The addition of bothDelta-1 and FP to cultures resulted in 216-fold, 22-fold, and 132-fold increases in the numbers of BFU-E, CFU-Mix, and CFU-GM, respectively, relative to freshly isolated cells. Delta-1 did not affect the generation of colony-forming cells in cultures without FP. Thus, Delta-1 and FP synergistically enhanced the generation of BFU-E from primitive hematopoietic progenitors in MPB. In the cultures of CB CD34+CD38- cells with SCF, flt-3 ligand, TPO [3GF], 3GF plus Delta-1, 3GF plus FP, and 3GF plus FP plus Delta-1, the synergistic enhancement by Delta-1 and FP was observed in the generation of BFU-E and CFU-Mix. These data suggest a novel role for interaction between Notch and gp130 signalings inthe generation of erythroid progenitors from primitive hematopoietic progenitors.

L10 ANSWER 20 OF 44 MEDLINE on STN

2004474599. PubMed ID: 15385170. R11: a cis-regulatory node of the sea urchin embryo gene network that controls early expression of SpDelta in micromeres. Revilla-i-Domingo Roger; Minokawa Takuya; Davidson Eric H. (Division of Biology 156-29, California Institute of Technology, Pasadena, CA 91125, USA.) Developmental biology, (2004 Oct 15) Vol. 274, No. 2, pp. 438-51. Journal code: 0372762. ISSN: 0012-1606. (Investigators: Davidson E H, CA Inst Technol, Pasadena) Pub. country: United States. Language: English.

AB A gene regulatory network (GRN) controls the process by which the endomesoderm of the sea urchin embryo is specified. In this GRN, the program of gene expression unique to the skeletogenic micromere lineage is set in train by activation of the pmar1 gene. Through a double repression system, this gene is responsible for localization of expression of downstream regulatory and signaling genes to cells of this lineage. One of these genes, delta, encodes a **Notch ligand**, and its expression in the right place and time is crucial to the specification of the endomesoderm. Here we report a cis-regulatory element R11 that is responsible for localizing the expression of delta by means of its response to the pmar1 repression system. R11 was identified as an evolutionarily conserved genomic sequence located about 13 kb downstream of the last exon of the delta gene. We demonstrate here that this cis-regulatory element is able to drive the expression of a reporter gene in the same cells and at the same time that the endogenous delta gene is expressed, and that temporally, spatially, and quantitatively it responds to the pmar1 repression system just as predicted for the delta gene in the endomesoderm GRN. This work illustrates the application of cis-regulatory analysis to the validation of predictions of the GRN model. In addition, we introduce new methodological tools for quantitative measurement of the output of expression constructs that promise to be of general value for cis-regulatory analysis in sea urchin embryos.

L10 ANSWER 21 OF 44 CAPLUS COPYRIGHT 2007 ACS on STN

2003:837139 Document No. 139:336935 Particle-bound Notch pathway-modifying immunomodulators for immunotherapy of cancer, allergy, infection, inflammation, and autoimmune disease and for modulator screening. Bodmer, Mark William; Briend, Emmanuel Cyrille Pascal; Champion, Brian Robert; Lennard, Andrew Christopher; McKenzie, Grahame James; Tugal, Tamara; Ward, George Albert; Young, Lesley Lynn (Lorantis Limited, UK). PCT Int. Appl. WO 2003087159 A2 20031023, 177 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,

MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-GB1525 20030404. PRIORITY: GB 2002-7930 20020405; GB 2002-7929 20020405; GB 2002-12282 20020528; GB 2002-12283 20020528; WO 2002-GB3397 20020725; WO 2002-GB3426 20020725; GB 2002-20913 20020910; GB 2002-20912 20020910; GB 2003-234 20030107.

AB A method is disclosed for therapeutic modulation of Notch signalling by administering modulators of the Notch signal transduction pathway bound to a pharmaceutically acceptable carrier. The modulators may be in mixts. of up to 100 different entities. The modulators may also be conjugated with one another, e.g. in **fusion proteins**. The construction of a CHO-derived cell line carrying a Notch pathway-dependent luciferase reporter gene to screen for **Notch ligands** is described.

L10 ANSWER 22 OF 44 CAPLUS COPYRIGHT 2007 ACS on STN

2003:591212 Document No. 139:143996 Protein and cDNA sequences of human PDZ-RGS proteins and use in modulating Notch signalling pathway. Champion, Brian Robert; Falciani, Francesco; Hayward, Penelope Caroline; Maslen, Gareth Llewellyn (Lorantis Limited, UK). PCT Int. Appl. WO 2003062273 A2 20030731, 136 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-GB303 20030127. PRIORITY: GB 2002-1674 20020125.

AB The invention provides protein and cDNA sequences of human PDZ-RGS proteins. A method is described for modifying chemokine signalling by administering an effective amount of a modulator of the Notch signalling pathway. Human homologues of certain proteins, polypeptides and polynucleotides involved in Notch and/or chemokine signalling pathways are also described.

L10 ANSWER 23 OF 44 CAPLUS COPYRIGHT 2007 ACS on STN

2003:396917 Document No. 138:396198 **Fusion proteins** comprising human Delta or Jagged proteins as inhibitors of the Notch signalling pathway and uses in cancer therapy. Bodmer, Mark William; Briend, Emmanuel Cyrille Pascal; Champion, Brian Robert; Lennard, Andrew Christopher; McKenzie, Grahame James; Ragno, Silvia; Tugal, Tamara; Young, Lesley Lynn (Lorantis Limited, UK). PCT Int. Appl. WO 2003042246 A2 20030522, 217 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-GB5133 20021113. PRIORITY: GB 2001-27271 20011114; GB 2002-20913 20020910.

AB The present invention provides **fusion proteins** comprising human Delta protein or Jagged protein fused with IgG as inhibitors of the Notch signalling pathway and their therapeutic uses. Specifically, the invention provides (i) a protein or polypeptide which comprises a **Notch ligand** DSL domain and 0, 1 or 2 but no more than 2 **Notch ligand** EGF-like domains; (ii) a multimer of such a protein or polypeptide (wherein each monomer may be the

same or different); or (iii) a polynucleotide coding for such a protein or polypeptide; for use in the treatment of cancer. The present invention seeks to provide further methods for treating cancer and, in particular, for promoting immune responses to cancer, in particular by modification of Notch-**Notch ligand** interaction.

L10 ANSWER 24 OF 44 CAPLUS COPYRIGHT 2007 ACS on STN
2003:396736 Document No. 138:400396 Composition comprising inhibitors of Notch signaling pathway and pathogen antigen for vaccination against infection. Bodmer, Mark William; Briend, Emmanuel Cyrille Pascal; Champion, Brian Robert; Lennard, Andrew Christopher; McKenzie, Grahame James; Ragno, Silvia; Tugal, Tamara; Young, Lesley Lynn (Lorantis Limited, UK). PCT Int. Appl. WO 2003041735 A2 20030522, 254 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-GB5137 20021113. PRIORITY: GB 2001-27267 20011114; WO 2002-GB3426 20020725; GB 2002-20849 20020907; GB 2002-20913 20020910; WO 2002-GB4390 20020927.
AB An inhibitor of the Notch signalling pathway is used in the manufacture of a medicament for use as an immunostimulant, for example as a vaccine adjuvant. The **Notch ligand** or receptor antagonists may comprise DSL domain of human Delta1, Delta3, or Delta4, extracellular domain of human Serrate or Jagged (Jagged 1 and 2), or EGF11 or EGF12 of human Notch1, Notch2, Notch3 or Notch4. These Notch inhibitors are capable of reducing the ability of **Notch ligand** to bind and/or activate Notch receptor on immune cells, and are capable of increasing activity of T cells, e.g. regulatory T cells, helper T cells, cytotoxic T lymphocytes, and effector T cells. The Notch signaling inhibitors are used in combination with antigen for vaccination against infection or chronic infection by pathogen such as bacteria, virus, fungus or parasite.

L10 ANSWER 25 OF 44 CAPLUS COPYRIGHT 2007 ACS on STN
2003:282609 Document No. 138:302663 Immunomodulators modifying Notch signalling pathway for immunotherapy and modulator screening. Briend, Emmanuel Cyrille Pascal; Champion, Brian Robert; Solari, Roberto Celeste Ercole (Lorantis Limited, UK). PCT Int. Appl. WO 2003029293 A2 20030410, 130 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-GB4390 20020927. PRIORITY: GB 2001-23379 20010928.
AB Use of a modulator of Notch IC protease activity in the manufacture of a medicament for use in immunotherapy and methods of detecting such a modulator. The Notch IC protease modulator includes agonist or antagonist of presenilin or presenilin-dependent γ-secretase. The Notch IC protease modulators are optionally in combination with Notch signalling pathway up-regulating agent (e.g. **Notch ligands**, Noggin, Chordin, follistatin, Xnr3, FGF and derivs.), or down-regulating agent (e.g. Toll-like receptor, cytokine, bone morphogenetic protein or BMP, BMP receptor, activin, or nucleic acid encoding them). The Notch signalling pathway modulators are useful for immunotherapy of allergy, inflammation, infection, autoimmune disease, graft rejection, cancer, and

other T cell-mediated disease.

L10 ANSWER 26 OF 44 CAPLUS COPYRIGHT 2007 ACS on STN
2003:118018 Document No. 138:168835 Targeting of an antigen presenting cell (APC) with a modulator of T cell signalling, such as a **Notch ligand**, coupled to the MHC class II-binding motif from a superantigen. Bodmer, Mark William; Champion, Brian Robert; McKenzie, Grahame James; Nye, Lucy Emma (Lorantis Limited, UK). PCT Int. Appl. WO 2003012111 A2 20030213, 93 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-GB3381 20020725. PRIORITY: GB 2001-18155 20010725.
AB The present invention relates to the concept of delivering a modulator of T cell signaling, such as a **Notch ligand**, to an antigen presenting cell (APC). The targeting approach disclosed uses, for example, the major histocompatibility complex (MHC) class II binding motif from a superantigen coupled to a modulator of the Notch signaling pathway. Superantigens bind both MHC class II mols. and subsets of T cell receptors and thus effectively cross-link APCs to T cells and activate cells polyclonally. The mol. regions of these mols. that impart T cell receptor (TCR) and MHC class II binding have been defined structurally and have been shown to be distinct regions of the mol. By using the MHC class II binding domain with a modulator of the Notch signaling pathway we can focus the activity of the Notch signaling pathway modulator to the APCs at the site of delivery. Further, the domain lacks toxin activity because it cannot find the T cell receptor to activate T cells. According to one aspect of the present invention there is provided a conjugate comprising a first and a second sequence wherein the first sequence comprises a polypeptide which is capable of binding to an APC, or a polynucleotide encoding therefor, and the second sequence comprises a polypeptide comprising a modulator of a signaling pathway in a T cell or a polynucleotide encoding therefor.

L10 ANSWER 27 OF 44 CAPLUS COPYRIGHT 2007 ACS on STN
2003:117645 Document No. 138:163535 Modulators of Notch signalling for use in immunotherapy. Bodmer, Mark William; Briend, Emmanuel Cyrille Pascal; Champion, Brian Robert; Young, Lesley Lynn (Lorantis Limited, UK). PCT Int. Appl. WO 2003011317 A1 20030213, 182 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-GB3426 20020725. PRIORITY: GB 2001-18153 20010725; GB 2002-7930 20020405; GB 2002-12282 20020528; GB 2002-12283 20020528.
AB The present invention provides new uses of modulators of Notch signaling in therapy and corresponding methods of treatment. The modulators of Notch signaling can be used to modulate immune cytokine expression in various cells for treatment of various diseases.

L10 ANSWER 28 OF 44 MEDLINE on STN
2003073185. PubMed ID: 12411302. Combined effects of Notch signaling and cytokines induce a multiple log increase in precursors with lymphoid and myeloid reconstituting ability. Varnum-Finney Barbara; Brashem-Stein

Carolyn; Bernstein Irwin D. (Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA.) Blood, (2003 Mar 1) Vol. 101, No. 5, pp. 1784-9. Electronic Publication: 2002-10-31. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB We investigated whether combined signaling induced by engineered **Notch ligands** and hematopoietic growth factors influences hematopoietic stem-cell differentiation. We show that incubation of murine marrow precursors with Delta1(ext-IgG), a **Notch ligand** consisting of the Delta1 extracellular domain fused to the Fc portion of human immunoglobulin G1 (IgG1), and growth factors stem cell factor (SCF), interleukin 6 (IL-6), IL-11, and Flt3-l inhibited myeloid differentiation and promoted a several-log increase in the number of precursors capable of short-term lymphoid and myeloid repopulation. Addition of IL7 promoted early T-cell development, whereas addition of granulocyte-macrophage colony-stimulating factor (GM-CSF) led to terminal myeloid differentiation. These results support a role for combinatorial effects by Notch and cytokine-induced signaling pathways in regulating hematopoietic cell fate and suggest the usefulness of **Notch ligand** in increasing hematopoietic precursor numbers for clinical stem-cell transplantation.

L10 ANSWER 29 OF 44 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN

2003:1096918 The Genuine Article (R) Number: 751VY. Acute myeloid leukemia **fusion proteins** deregulate genes involved in stem cell maintenance and DNA repair. Alcalay M (Reprint); Meani N; Gelmetti V; Fantozzi A; Fagioli M; Orleth A; Riganelli D; Sebastiani C; Cappelli E; Casciari C; Sciurpi M T; Mariano A R; Minardi S P; Luzi L; Muller H; Di Fiore P P; Frosina G; Pelicci P G. IFOM, Via Adamello 16, I-20139 Milan, Italy (Reprint); IFOM, I-20139 Milan, Italy; European Inst Oncol, Dept Expt Oncol, Milan, Italy; Univ Perugia, Dept Clin & Expt Med, Monteluce Policlin, I-06100 Perugia, Italy; Ist Nazl Ric Canc, DNA Repair Unit, Mutagenesis Lab, Genoa, Italy. JOURNAL OF CLINICAL INVESTIGATION (DEC 2003) Vol. 112, No. 11, pp. 1751-1761. ISSN: 0021-9738. Publisher: AMER SOC CLINICAL INVESTIGATION INC, 35 RESEARCH DR, STE 300, ANN ARBOR, MI 48103 USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Acute myelogenous leukemias (AMLs) are genetically heterogeneous and characterized by chromosomal rearrangements that produce **fusion proteins** with aberrant transcriptional regulatory activities. Expression of AML **fusion proteins** in transgenic mice increases the risk of myeloid leukemias, suggesting that they induce a preleukemic state. The underlying molecular and biological mechanisms are, however, unknown. To address this issue, we performed a systematic analysis of **fusion protein** transcriptional targets. We expressed AML1/ETO, PML/RAR, and PLZF/RAR in U937 hemopoietic precursor cells and measured global gene expression using oligonucleotide chips. We identified 1,555 genes regulated concordantly by at least two **fusion proteins** that were further validated in patient samples and finally classified according to available functional information. Strikingly, we found that AML **fusion proteins** induce genes involved in the maintenance of the stem cell phenotype and repress DNA repair genes, mainly of the base excision repair pathway. Functional studies confirmed that ectopic expression of **fusion proteins** constitutively activates pathways leading to increased stem cell renewal (e.g., the Jagged1/Notch pathway) and provokes accumulation of DNA damage. We propose that expansion of the stem cell compartment and induction of a mutator phenotype are relevant features underlying the leukemic potential of AML-associated **fusion proteins**.

L10 ANSWER 30 OF 44 MEDLINE on STN

2003571944. PubMed ID: 14645852. Notch-mediated restoration of regenerative potential to aged muscle. Conboy Irina M; Conboy Michael J; Smythe Gayle M; Rando Thomas A. (Department of Neurology and Neurological Sciences, Stanford University School of Medicine, Stanford, CA 94305-5235, USA.) Science (New York, N.Y.), (2003 Nov 28) Vol. 302, No. 5650, pp. 1575-7. Journal code: 0404511. E-ISSN: 1095-9203. Pub. country: United States. Language: English.

AB A hallmark of aging is diminished regenerative potential of tissues, but the mechanism of this decline is unknown. Analysis of injured muscle revealed that, with age, resident precursor cells (satellite cells) had a markedly impaired propensity to proliferate and to produce myoblasts necessary for muscle regeneration. This was due to insufficient up-regulation of the **Notch ligand** Delta and, thus, diminished activation of Notch in aged, regenerating muscle. Inhibition of Notch impaired regeneration of young muscle, whereas forced activation of Notch restored regenerative potential to old muscle. Thus, Notch signaling is a key determinant of muscle regenerative potential that declines with age.

L10 ANSWER 31 OF 44 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2003305179 EMBASE Immunology - 15th European Congress 8-12 June 2003, Rhodes, Greece. Contrafouris Y.. Y. Contrafouris, Thomson Current Drugs, Middlesex House, 34-42 Cleveland Street, London W1T 4JE, United Kingdom. yiannos.contrafouris@current-drugs.com. IDrugs Vol. 6, No. 7, pp. 647-649 1 Jul 2003.
ISSN: 1369-7056. CODEN: IDRUFN
Pub. Country: United Kingdom. Language: English. Summary Language: English.
Entered STN: 20030814. Last Updated on STN: 20030814

AB The Congress offered an impressive, if not daunting, amount of scientific information, and succeeded in bringing together scientists from research centers across Europe. Although the organizers, the EFIS, did not provide information on the next European Immunology Congress, Paris will host the first Paneuropean Immunology Congress in 2006. There are still a great number of questions to be addressed regarding human immune responses. It is unlikely that all of them will be answered in the next few years; however, judging from the quality of this year's Congress, the scientific world has definitely become better equipped to combat a host of conditions affecting immunity.

L10 ANSWER 32 OF 44 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

2004:150983 Document No.: PREV200400147265. Inhibition of vascular endothelium by the **Notch-ligand** delta-4 unveils a novel therapeutic target. Tavares, Maria J. [Reprint Author]; Freeman, Gordon J. [Reprint Author]; van Grotel, Martine [Reprint Author]; Henrique, Domingos; Carlesso, Nadia; Nadler, Lee M. [Reprint Author]; Cardoso, Angelo A. [Reprint Author]. Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA. Blood, (November 16 2003) Vol. 102, No. 11, pp. 531a. print.
Meeting Info.: 45th Annual Meeting of the American Society of Hematology. San Diego, CA, USA. December 06-09, 2003. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971. Language: English.

AB The identification of targets specifically influencing the formation and maintenance of the vasculature has great potential for the treatment of cancer and other disorders. Normal and tumor-associated neovascularization is tightly regulated by a series of positive and negative signals. Studies in deficient mice revealed that abrogation of Notch signaling leads to extensive defects in vascular development and remodeling, thus implying Notch as a positive regulator. Also, the expression of Notch-4 and the ligand Dll4 is largely restricted to

endothelium. However, little is known about how Notch regulates vascular endothelium and neovascularization. To dissect the role of Notch signaling, we cloned the human homologue of Dll4 and evaluated its functional and biochemical properties in human vascular endothelial cells (HUVEC). A Dll4-Ig **fusion protein** effectively binds to HUVEC, which express both receptors for Dll4, Notch-1 and Notch-4. Dll4-Ig is biologically active, inducing the cleavage of Notch-1 (Notchic) and the activation of the Notch downstream target HES, as observed by RT-PCR and reporter assays. Surprisingly, functional studies showed that Dll4-Ig significantly inhibit cell proliferation (p=0.01), as assessed by MTS assays. This inhibitory effect was not mediated by cell apoptosis but rather by Dll4-induced cell cycle arrest of endothelial cells in G0/G1 phase (p=0.01). Biochemical analysis of cell cycle regulatory elements showed that Dll4-Ig mediates downregulation of Cyclin D1 and pCDK2 as well as a significant decrease of Rb phosphorylation. Also, Dll4-mediated engagement of Notch signaling in HUVEC affected the kinase activity of CDK2 and CDK4. In contrast to other cellular contexts, activation of Notch signaling in HUVEC did not trigger significant changes in the expression of the CDK inhibitor p27kip1. Finally, gene profiling revealed that Dll4-Ig binding to HUVEC induces a series of changes in the expression of genes linked to cell poliferation, as well as signaling pathways implicated in vascular biology, such as Eph/ephrins and TGF-b. This study provides the first evidence that the engagement of Notch signaling through Dll4 may function as a negative regulator of vascular endothelial cell growth. It also suggests that Notch signaling may serve as valid therapeutic target and that the development of effective Dll4 agonists may provide new tools for the treatment of vascular proliferative disorders and tumor angiogenesis.

L10 ANSWER 33 OF 44 CAPLUS COPYRIGHT 2007 ACS on STN
2003:149776 Document No. 140:26146 t(11;19)(q21;p13) translocation in mucoepidermoid carcinoma creates a novel fusion product that disrupts a Notch signaling pathway. [Erratum to document cited in CA138:318526]. Tonon, Giovanni; Modi, Sanjay; Wu, Lizi; Kubo, Akihito; Coxon, Amy B.; Komiya, Takefumi; O'Neil, Kevin; Stover, Kristen; El-Naggar, Adel; Griffin, James D.; Kirsch, Ilan R.; Kaye, Frederic J. (Center for Cancer Research, Genetics Branch, National Cancer Institute and the National Naval Medical Center, Bethesda, MD, 20889, USA). Nature Genetics, 33(3), 430 (English) 2003. CODEN: NGENEC. ISSN: 1061-4036. Publisher: Nature Publishing Group.
AB In Figure 5c, C21orf33 should read HES1, and in Figure 5d, HRY should read HES1. The corrected version of Figure 5 is given.

L10 ANSWER 34 OF 44 MEDLINE on STN
2003316064. PubMed ID: 12844399. The extracellular domain of human delta-like-1 expressed and purified from CHO cells promotes expansion of hematopoietic progenitor cells. Lu Zhuo-Zhuang; Wu Chu-Tse; Liu Hong-Jun; Zhang Qun-Wei; Jia Xiang-Xu; Wang Li-Sheng. (Institute of Radiation Medicine, Academy of Military Medical Sciences, Beijing 100850, China.) Zhongguo shi yan xue ye xue za zhi / Zhongguo bing li sheng li xue hui = Journal of experimental hematology / Chinese Association of Pathophysiology, (2003 Jun) Vol. 11, No. 3, pp. 222-6. Journal code: 101084424. ISSN: 1009-2137. Pub. country: China. Language: Chinese.
AB Notch signal path plays important roles in the regulation of proliferation and differentiation of hematopoietic stem cells. An extracellular domain of human Delta-like-1 (hDll-1(ext)), one of **Notch ligands**, was cloned and expressed in CHO cells, and the effect of hDll-1(ext) on expansion of hematopoietic stem/progenitor cells was investigated in this study. Total RNA was isolated from human marrow mononuclear cells. hDll-1(ext) was amplified by RT-PCR and cloned to T vector, then the gene was sequenced and subcloned to pcDNA3.1/Myc-His(+)A expression vector. The constructed plasmid was transfected into CHO cells

with lipofectin and the expression of secreted hDll-1(ext) in G418-resistant clones was assayed by Western blot. hDll-1(ext) high-expressed clone was cultured to collect supernatant. **Fusion protein** hDll-1(ext) was purified from the supernatant by immobilized metal affinity chromatography (IMAC). The results showed that expression of Notch-1 receptor was detected in cord blood-derived CD34(+) cells by RT-PCR. Human umbilical blood CD34(+) cells were cultured in serum-free medium containing SCF, IL-3, VEGF, and with or without purified hDll-1(ext) for 4 or 8 days. Effect of hDll-1(ext) on the expansion of progenitor cells was analyzed then by clonogenic assays. The number of CFU-Mix and HPP-CFC generated from the culture system containing hDll-1(ext) was 1.5 times of that from the control. In conclusion, the recombinant hDll-1(ext) promotes the expansion of primitive hematopoietic progenitors.

L10 ANSWER 35 OF 44 CAPLUS COPYRIGHT 2007 ACS on STN
2003:75078 Document No. 138:318526 t(11;19)(q21;p13) translocation in mucoepidermoid carcinoma creates a novel fusion product that disrupts a Notch signaling pathway. Tonon, Giovanni; Modi, Sanjay; Wu, Lizi; Kubo, Akihito; Coxon, Amy B.; Komiya, Takefumi; O'Neil, Kevin; Stover, Kristen; El-Naggar, Adel; Griffin, James D.; Kirsch, Ilan R.; Kaye, Frederic J. (Center for Cancer Research, Genetics Branch, National Cancer Institute and the National Naval Medical Center, Bethesda, MD, 20889, USA). Nature Genetics, 33(2), 208-213 (English) 2003. CODEN: NGENEC. ISSN: 1061-4036. Publisher: Nature Publishing Group.
AB Truncation of Notch1 has been shown to cause a subtype of acute leukemia, and activation of Notch4 has been associated with mammary and salivary gland carcinomas of mice. Here we identify a new mechanism for disrupting Notch signaling in human tumorigenesis, characterized by altered function of a new ortholog of the Drosophila melanogaster Notch co-activator mol. Mastermind. We cloned the t(11;19) translocation that underlies the most common type of human malignant salivary gland tumor. This rearrangement fuses exon 1 from a novel gene of unknown function at 19p13, termed mucoepidermoid carcinoma translocated 1 (MECT1), with exons 2-5 of a novel member of the Mastermind-like gene family (MAML2) at 11q21 (reference 3). Similar to D. melanogaster Mastermind and MAML1, full-length MAML2 functioned as a CSL (CBF-1, suppressor of hairless and Lag-1)-dependent transcriptional co-activator for ligand-stimulated Notch. In contrast, MECT1-MAML2 activated transcription of the Notch target gene HES1 independently of both **Notch ligand** and CSL binding sites. MECT1-MAML2 induced foci formation in RK3E epithelial cells, confirming a biol. effect for the fusion product. These data suggest a new mechanism to disrupt the function of a Notch co-activator in a common type of malignant salivary gland tumor.

L10 ANSWER 36 OF 44 MEDLINE on STN
2001440175. PubMed ID: 11486045. HERP, a novel heterodimer partner of HES/E(spl) in Notch signaling. Iso T; Sartorelli V; Poizat C; Iezzi S; Wu H Y; Chung G; Kedes L; Hamamori Y. (Institute for Genetic Medicine, Keck School of Medicine of the University of Southern California, Los Angeles, CA 90089-9075, USA.) Molecular and cellular biology, (2001 Sep) Vol. 21, No. 17, pp. 6080-9. Journal code: 8109087. ISSN: 0270-7306. Pub. country: United States. Language: English.
AB HERP1 and -2 are members of a new basic helix-loop-helix (bHLH) protein family closely related to HES/E(spl), the only previously known Notch effector. Like that of HES, HERP mRNA expression is directly up-regulated by **Notch ligand** binding without de novo protein synthesis. HES and HERP are individually expressed in certain cells, but they are also coexpressed within single cells after Notch stimulation. Here, we show that HERP has intrinsic transcriptional repression activity. Transcriptional repression by HES/E(spl) entails the recruitment of the corepressor TLE/Groucho via a conserved WRPW motif, whereas unexpectedly

the corresponding-but modified-tetrapeptide motif in HERP confers marginal repression. Rather, HERP uses its bHLH domain to recruit the mSin3 complex containing histone deacetylase HDAC1 and an additional corepressor, N-CoR, to mediate repression. HES and HERP homodimers bind similar DNA sequences, but with distinct sequence preferences, and they repress transcription from specific DNA binding sites. Importantly, HES and HERP associate with each other in solution and form a stable HES-HERP heterodimer upon DNA binding. HES-HERP heterodimers have both a greater DNA binding activity and a stronger repression activity than do the respective homodimers. Thus, Notch signaling relies on cooperation between HES and HERP, two transcriptional repressors with distinctive repression mechanisms which, either as homo- or as heterodimers, regulate target gene expression.

L10 ANSWER 37 OF 44 MEDLINE on STN
2001477008. PubMed ID: 11520788. The **Notch ligand**, Delta-1, inhibits the differentiation of monocytes into macrophages but permits their differentiation into dendritic cells. Ohishi K; Varnum-Finney B; Serda R E; Anasetti C; Bernstein I D. (Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA.) Blood, (2001 Sep 1) Vol. 98, No. 5, pp. 1402-7. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.
AB Notch-mediated cellular interactions are known to regulate cell fate decisions in various developmental systems. A previous report indicated that monocytes express relatively high amounts of Notch-1 and Notch-2 and that the immobilized extracellular domain of the **Notch ligand**, Delta-1 (Delta(ext-myc)), induces apoptosis in peripheral blood monocytes cultured with macrophage colony-stimulating factor (M-CSF), but not granulocyte-macrophage CSF (GM-CSF). The present study determined the effect of Notch signaling on monocyte differentiation into macrophages and dendritic cells. Results showed that immobilized Delta(ext-myc) inhibited differentiation of monocytes into mature macrophages (CD1a+/-CD14+/- CD64+) with GM-CSF. However, Delta(ext-myc) permitted differentiation into immature dendritic cells (CD1a+CD14-CD64-) with GM-CSF and interleukin 4 (IL-4), and further differentiation into mature dendritic cells (CD1a+CD83+) with GM-CSF, IL-4, and tumor necrosis factor-alpha (TNF-alpha). Notch signaling affected the differentiation of CD1a-CD14+ macrophage/dendritic cell precursors derived in vitro from CD34+ cells. With GM-CSF and TNF-alpha, exposure to Delta(ext-myc) increased the proportion of precursors that differentiated into CD1a+CD14- dendritic cells (51% in the presence of Delta(ext-myc) versus 10% in control cultures), whereas a decreased proportion differentiated into CD1a-CD14+ macrophages (6% versus 65%). These data indicate a role for Notch signaling in regulating cell fate decisions by bipotent macrophage/dendritic precursors.

L10 ANSWER 38 OF 44 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
2002:129745 Document No.: PREV200200129745. The soluble **Notch ligand**, Jagged-1, inhibits proliferation of CD34+ macrophage progenitors. Araki, Hiroto [Reprint author]; Katayama, Naoyuki [Reprint author]; Masuya, Masahiro [Reprint author]; Hoshino, Natsuki [Reprint author]; Miyashita, Hiroyuki [Reprint author]; Sakano, Seiji; Yamaguchi, Motoko [Reprint author]; Nishii, Kazuhiro [Reprint author]; Minami, Nobuyuki; Shiku, Hiroshi [Reprint author]. Second Department of Internal Medicine, Mie University School of Medicine, Tsu, Mie, Japan. Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 74a. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1. Orlando, Florida, USA. December 07-11, 2001. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971. Language: English.
AB The Notch/**Notch ligand** system controls diverse

cellular processes and cell fate dicisions in various organisms. The proteolytic cleavage generates transmembrane and soluble forms of **Notch ligands**. Although the function of transmembrane form of **Notch ligands** has been extensively studied, the role of their soluble form in human hematopoiesis is not well understood. As we detected the expression of Notch receptors, Notch-1 and Notch-2, on cord blood CD34+ cells as determined by flowcytometry, the activity of a soluble **Notch ligand**, human Jagged-1, was examined under serum-deprived conditions, using soluble human Jagged-1-IgG1 chimera protein (hJagged-1). Soluble hJagged-1 alone was not effective for colony formation by human cord blood CD34+ cells. Soluble hJagged-1 inhibited myeloid colony formation but not erythroid-mix or erythroid colony formation, in the presence of stem cell factor (SCF), IL-3, GM-CSF, G-CSF, thrombopoietin, and erythropoietin, in a dose-dependent manner. The inhibitory effects of soluble hJagged-1 on colony formation reached a minimal plateau at the concentration of 0.5 to 1 mg/ml. Cytological analysis revealed that the inhibition of myeloid colony formation by soluble hJagged-1 was mainly due to a decrease in the number of macrophage colony. Among various two-factor combinations, we found that M-CSF plus SCF, M-CSF plus IL-6, M-CSF plus flt3 ligand, and GM-CSF plus SCF predominantly supported the growth of CFU-M in our culture system. Using these two-factor combinations, we analyzed the effects of soluble hJagged-1 on colony formation. Soluble hJagged-1 led to an inhibition of macrophage colony formation supported by M-CSF plus SCF and GM-CSF plus SCF. The inhibition of CFU-M formation was not observed when soluble hJagged-1 was added to cultures after day 2 of incubation. The suppression of CFU-M formation was not associated with a decrease in colony size. These data demonstrated that soluble hJagged-1 inhibited the growth of macrophage progenitors by acting at the early stage of macrophage development. Direct action of hJagged-1 on CD34+ cells was confirmed by the expression of Hairy Enhancer of Split-1, HES-1. These results suggest that soluble hJagged-1 may regulate human hematopoiesis in the monocyte-macrophage lineage.

L10 ANSWER 39 OF 44 MEDLINE on STN

2000296681. PubMed ID: 10835354. Notch signalling via RBP-J promotes myeloid differentiation. Schroeder T; Just U. (GSF, National Research Centre for Environment and Health, Institute for Clinical Molecular Biology, Marchioninistrabetae 25, D-81377 Munich, Germany.) The EMBO journal, (2000 Jun 1) Vol. 19, No. 11, pp. 2558-68. Journal code: 8208664. ISSN: 0261-4189. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The expression of Notch receptors on hematopoietic cells and of cognate ligands on bone marrow stromal cells suggests a possible role for Notch signalling in the regulation of hematopoiesis. In order to assess the involvement of Notch1 signalling in myelopoiesis, 32D myeloid progenitor cell lines were engineered to permit the conditional induction of the constitutively active intracellular domain of murine Notch1 (mN1(IC)) by the 4-hydroxytamoxifen-inducible system. The induction of mN1(IC) resulted in accelerated and increased granulocytic differentiation. These effects were observed under growth conditions that support differentiation and, to a lesser degree, under conditions that normally promote self-renewal. Transient transfection of mN1(IC) deletion mutants showed that the differentiation promoting activity correlated with RBP-J transactivation. Furthermore, expression of a transcriptionally active derivative of RBP-J (RBP-J-VP16) increased myeloid differentiation. To test further the role of Notch signalling in a physiological context, 32D cells expressing mNotch1 were cultured on fibroblast layers that either expressed or did not express the **Notch ligand** Jagged1. Similar to the induction of mN1(IC), Jagged1 accelerated granulocytic differentiation of 32D cells. Taken together, our data suggest that activation of mNotch1 promotes myeloid differentiation via RBP-J

transactivation.

L10 ANSWER 40 OF 44 MEDLINE on STN
2000155994. PubMed ID: 10688816. A soluble form of human Delta-like-1 inhibits differentiation of hematopoietic progenitor cells. Han W; Ye Q; Moore M A. (Laboratory of Developmental Hematopoiesis, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA.) Blood, (2000 Mar 1) Vol. 95, No. 5, pp. 1616-25. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.
AB Two **Notch ligand** families, Delta and Serrate/Jagged, have been identified in vertebrates. Members of the Jagged family have been shown to affect in vitro hematopoiesis. To determine whether members of the Delta family might play a similar role in hematopoiesis, we examined the expression of mouse Delta-like-1 (mDll1). mDll1 protein was detected in whole marrow and in a marrow stromal cell line MS-5. At the RNA level, both mDll1 and Notch1 were seen in marrow precursor, differentiated hematopoietic, marrow stromal, and MS-5 cells. We isolated a cDNA encoding the human homologue of mDll1, designated human Delta-like-1 (hDll1). A soluble form of hDll1, hDll1(NDSL), containing the DSL domain and the N-terminal sequences, was expressed and purified from bacteria as a glutathione S-transferase (GST) **fusion protein**. We observed that hDll1(NDSL) delayed the acquisition of differentiation markers by murine hematopoietic progenitor cells (Lin-) cultured in vitro with cytokines. In addition, it promoted greater expansion (more than 3 times) of the primitive hematopoietic precursor cell population, measured in high-proliferative potential colony assay and day 12 colony-forming unit spleen (CFU-S) assay, than GST controls. We also observed that the percentage of apoptotic cells decreased and that the number of cells in the S-phase of the cell cycle increased in the cultures of Lin(-) cells with hDll1(NDSL). The effects of hDll1(NDSL) were blocked by antibody against the mouse counterpart of hDll1(NDSL), mDll1(NDSL). These observations demonstrate that hDll1 plays a role in mediating cell fate decisions during hematopoiesis. (Blood. 2000;95:1616-1625)

L10 ANSWER 41 OF 44 MEDLINE on STN
2000306665. PubMed ID: 10850492. Transient Notch activation initiates an irreversible switch from neurogenesis to gliogenesis by neural crest stem cells. Morrison S J; Perez S E; Qiao Z; Verdi J M; Hicks C; Weinmaster G; Anderson D J. (Department of Internal Medicine, University of Michigan, Ann Arbor 48109, USA.) Cell, (2000 May 26) Vol. 101, No. 5, pp. 499-510. Journal code: 0413066. ISSN: 0092-8674. Pub. country: United States. Language: English.
AB The genesis of vertebrate peripheral ganglia poses the problem of how multipotent neural crest stem cells (NCSCs) can sequentially generate neurons and then glia in a local environment containing strong instructive neurogenic factors, such as BMP2. Here we show that **Notch ligands**, which are normally expressed on differentiating neuroblasts, can inhibit neurogenesis in NCSCs in a manner that is completely dominant to BMP2. Contrary to expectation, Notch activation did not maintain these stem cells in an uncommitted state or promote their self-renewal. Rather, even a transient activation of Notch was sufficient to cause a rapid and irreversible loss of neurogenic capacity accompanied by accelerated glial differentiation. These data suggest that **Notch ligands** expressed by neuroblasts may act positively to instruct a cell-heritable switch to gliogenesis in neighboring stem cells.

L10 ANSWER 42 OF 44 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
2001:75955 Document No.: PREV200100075955. Determinants of Notch activity in modulating NGF-induced neurite outgrowth in PC12 cells. Levy, O. A.

[Reprint author]; Lah, J. J.; Levey, A. I.. Emory Univ, Atlanta, GA, USA. Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-118.1. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 04-09, 2000. Society for Neuroscience.
ISSN: 0190-5295. Language: English.

AB During nervous system development, the Notch signaling pathway influences cell fate decisions, as well as neurite outgrowth in neurons after terminal differentiation. Notch signaling involves several downstream components, including CBF/RBP-J transcription factors and the presenilin genes, which are associated with early onset familial Alzheimer's disease (FAD). We have previously shown that constitutively active truncated Notch1 proteins (e.g. CN1) inhibit NGF-induced neurite outgrowth in PC12 cells. We performed several experiments to assess the importance of these downstream elements in mediating Notch's effect on neuritogenesis. To test the role of CBF/RBP-J activation, we stimulated RBP-J activity independently of Notch by expressing an RBP-J-VP16 **fusion protein**. RBP-J-VP16 and CN1 caused a similar reduction in neurite length, suggesting that RBP-J activation is important for CN1's attenuation of neurite extension. However, activation of full length Notch by co-culture with fibroblasts expressing the **Notch ligand** Delta did not cause a decrease in neurite length. This finding might be due to differences in the subcellular site of activation and/or the degree of Notch activation. Finally, we assessed the effect of expressing either wild type or mutant presenilin-1 (PS1) on the signaling activity of different Notch proteins. We found that wild type and mutant PS1 had differential effects on only a subset of Notch constructs, suggesting that FAD-linked mutations affect specific steps in the Notch signaling pathway.

L10 ANSWER 43 OF 44 MEDLINE on STN

1999120954. PubMed ID: 9920832. Notch1-induced delay of human hematopoietic progenitor cell differentiation is associated with altered cell cycle kinetics. Carlesso N; Aster J C; Sklar J; Scadden D T. (Department of Experimental Hematology, Partners AIDS Research Center and MGH Cancer Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA.) Blood, (1999 Feb 1) Vol. 93, No. 3, pp. 838-48. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB Hematopoiesis is a balance between proliferation and differentiation that may be modulated by environmental signals. Notch receptors and their ligands are highly conserved during evolution and have been shown to regulate cell fate decisions in multiple developmental systems. To assess whether Notch1 signaling may regulate human hematopoiesis to maintain cells in an immature state, we transduced a vesicular stomatitis virus G-protein (VSV-G) pseudo-typed bicistronic murine stem cell virus (MSCV)-based retroviral vector expressing a constitutively active form of Notch1 (ICN) and green fluorescence protein into the differentiation competent HL-60 cell line and primary cord blood-derived CD34(+) cells. In addition, we observed endogenous Notch1 expression on the surface of both HL-60 cells and primary CD34(+) cells, and therefore exposed cells to **Notch ligand** Jagged2, expressed on NIH3T3 cells. Both ligand-independent and ligand-dependent activation of Notch resulted in delayed acquisition of differentiation markers by HL-60 cells and cord blood CD34(+) cells. In addition, primary CD34(+) cells retained their ability to form immature colonies, colony-forming unit-mix (CFU-mix), whereas control cells lost this capacity. Activation of Notch1 correlated with a decrease in the fraction of HL-60 cells that were in G0/G1 phase before acquisition of a mature cell phenotype. This enhanced progression through G1 was noted despite preservation of the proliferative rate of the cells and the overall length of the cell cycle. These findings show that Notch1 activation delays human hematopoietic differentiation and suggest a

link of Notch differentiation effects with altered cell cycle kinetics.

L10 ANSWER 44 OF 44 MEDLINE on STN
96312925. PubMed ID: 8756291. The intracellular deletions of Delta and Serrate define dominant negative forms of the Drosophila **Notch ligands**. Sun X; Artavanis-Tsakonas S. (Howard Hughes Medical Institute, Yale University, New Haven, Connecticut 06536-0812, USA.) Development (Cambridge, England), (1996 Aug) Vol. 122, No. 8, pp. 2465-74. Journal code: 8701744. ISSN: 0950-1991. Pub. country: ENGLAND: United Kingdom. Language: English.

AB We examined the function of the intracellular domains of the two known Drosophila **Notch ligands**, Delta and Serrate, by expressing wild-type and mutant forms in the developing Drosophila eye under the sevenless promoter. The expression of intracellularly truncated forms of either Delta (sev-DlTM) or Serrate (sev-SerTM) leads to extra photoreceptor phenotypes, similar to the eye phenotypes associated with loss-of-function mutations of either Notch or Delta. Consistent with the notion that the truncated ligands reduce. Notch signalling activity, the eye phenotypes of sev-DlTM and sev-SerTM are enhanced by loss-of-function mutations in the Notch pathway elements, Notch, Delta, mastermind, deltex and groucho, but are suppressed by a duplication of Delta or mutations in Hairless, a negative regulator of the pathway. These observations were extended to the molecular level by demonstrating that the expression of Enhancer of split m delta, a target of Notch signalling, is down-regulated by the truncated ligands highly expressed in neighbouring cells. We conclude that the truncated ligands act as antagonists of Notch signalling.

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 NEWS 11  JUL 21  USGENE adds bibliographic and sequence information
 NEWS 12  JUL 28  EPFULL adds first-page images and applicant-cited
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=> s conjugate?
L1      601032 CONJUGATE?

=> s l1 and antibod?
L2      123941 L1 AND ANTIBOD?

=> s l2 and mannose receptor
L3          87 L2 AND MANNOSE RECEPTOR

=> s l3 and notch ligand
L4           1 L3 AND NOTCH LIGAND

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L4   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2009 ACS on STN
2003:118018   Document No. 138:168835  Targeting of an antigen presenting cell
     (APC) with a modulator of T cell signalling, such as a Notch
     ligand, coupled to the MHC class II-binding motif from a
     superantigen.  Bodmer, Mark William; Champion, Brian Robert; McKenzie,
     Grahame James; Nye, Lucy Emma (Lorantis Limited, UK).  PCT Int. Appl. WO
     2003012111 A2 20030213, 93 pp.  DESIGNATED STATES: W:  AE, AG, AL, AM, AT,
     AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM,
     DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
     KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX,
     MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN,
     TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF,
     CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML,
     MR, NE, NL, PT, SE, SN, TD, TG, TR.  (English).  CODEN: PIXXD2.
     APPLICATION: WO 2002-GB3381 20020725.  PRIORITY: GB 2001-18155 20010725.
AB   The present invention relates to the concept of delivering a modulator of
     T cell signaling, such as a Notch ligand, to an
     antigen presenting cell (APC).  The targeting approach disclosed uses, for
     example, the major histocompatibility complex (MHC) class II binding motif
     from a superantigen coupled to a modulator of the Notch signaling pathway.
     Superantigens bind both MHC class II mols. and subsets of T cell receptors
     and thus effectively cross-link APCs to T cells and activate cells
     polyclonally.  The mol. regions of these mols. that impart T cell receptor
     (TCR) and MHC class II binding have been defined structurally and have
     been shown to be distinct regions of the mol.  By using the MHC class II
     binding domain with a modulator of the Notch signaling pathway we can
     focus the activity of the Notch signaling pathway modulator to the APCs at
     the site of delivery.  Further, the domain lacks toxin activity because it
     cannot find the T cell receptor to activate T cells.  According to one
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aspect of the present invention there is provided a **conjugate** comprising a first and a second sequence wherein the first sequence comprises a polypeptide which is capable of binding to an APC, or a polynucleotide encoding therefor, and the second sequence comprises a polypeptide comprising a modulator of a signaling pathway in a T cell or a polynucleotide encoding therefor.

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=> s l3 and "human Delta 1"
L5           0 L3 AND "HUMAN DELTA 1"

=> s l3 and "human Delta 3"
L6           0 L3 AND "HUMAN DELTA 3"

=> s l3 and "human Delta 4"
L7           0 L3 AND "HUMAN DELTA 4"

=> s L3 and "human Jagged 1"
L8           0 L3 AND "HUMAN JAGGED 1"

=> s l3 and "human Jagged 2"
L9           0 L3 AND "HUMAN JAGGED 2"

=> s l3 and targeting
L10         21 L3 AND TARGETING

=> s l10 and antigen presenting cell
L11          9 L10 AND ANTIGEN PRESENTING CELL

=> dup remove l11
PROCESSING COMPLETED FOR L11
L12          8 DUP REMOVE L11 (1 DUPLICATE REMOVED)

=> d l12 1-8 cbib abs

L12  ANSWER 1 OF 8  CAPLUS  COPYRIGHT 2009 ACS on STN
2009:490356   Document No. 150:470504  Vaccine compositions and systems
     comprising nanocarriers for delivery to cells of immune systems.  Von
     Andrian, Ulrich H.; Farokhzad, Omid C.; Langer, Robert S.; Junt, Tobias;
     Moseman, Ashley; Zhang, Liangfang; Basto, Pamela; Iannacone, Matteo;
     Alexis, Frank (Massachusetts Institute of Technology, USA).  PCT Int.
     Appl. WO 2009051837 A2 20090423, 256pp.  DESIGNATED STATES: W:  AE, AG,
     AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO,
     CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM,
     GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC,
     LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG,
     NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM,
     ST, SV, SY, TJ, TM, TN, TR; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY,
     DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, MT, NE, NL,
     NO, PT, SE, SN, TD, TG, TR.  (English).  CODEN: PIXXD2.  APPLICATION: WO
     2008-US11932 20081012.  PRIORITY: US 2007-979596P 20071012.
AB   The present invention provides compns. and systems for delivery of
     nanocarriers to cells of the immune system.  The invention provides
     vaccine nanocarriers capable of stimulating an immune response in T cells
     and/or in B cells, in some embodiments, comprising at least one
     immunomodulatory agent, and optionally comprising at least one
     targeting moiety and optionally at least one immunostimulatory
     agent.  The invention provides pharmaceutical compns. comprising inventive
     vaccine nanocarriers.  The present invention provides methods of
     designing, manufacturing, and using inventive vaccine nanocarriers and
     pharmaceutical compns. thereof.  The invention provides methods of
     prophylaxis and/or treatment of diseases, disorders, and conditions
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comprising administering at least one inventive vaccine nanocarrier to a subject in need thereof.

L12 ANSWER 2 OF 8 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN

2008577129 EMBASE Enhanced immune stimulation by a therapeutic lymphoma tumor antigen vaccine produced in insect cells involves **mannose receptor targeting** to **antigen presenting cells**.

Betting, David J.; Kafi, Kamran; Timmerman, John M. (correspondence). Division of Hematology and Oncology, Department of Medicine, University of California, Los Angeles, Los Angeles, CA, United States. jtimmerman@mednet.ucla.edu. Mu, Xi Y.; McDonnel, Desmond; Rosas, Francisco; Gold, Daniel P.. Favrille Inc., San Diego, CA, United States.

Vaccine Vol. 27, No. 2, pp. 250-259 7 Jan 2009.

Refs: 48.

ISSN: 0264-410X. CODEN: VACCDE.

Elsevier Ltd, Langford Lane, Kidlington, Oxford, OX5 1GB, United Kingdom.

S 0264-410X(08)01441-2. Pub. Country: United Kingdom. Language: English. Summary Language: English.

Entered STN: 20090122. Last Updated on STN: 20090122

AB Therapeutic vaccination of lymphoma patients with tumor-specific immunoglobulin (idiotype, Id) coupled to the carrier protein keyhole limpet hemocyanin (Id-KLH) is undergoing clinical investigation, and methods to improve the immunogenicity of these and other protein tumor antigen vaccines are being sought. Id proteins can be produced via tumor-myeloma hybridomas or recombinant methods in mammalian, bacteria, or insect cells. We now demonstrate that terminal mannose residues, characteristic of recombinant proteins produced in insect cells, yield Id proteins with significantly enhanced immunostimulatory properties compared to Id proteins derived from mammalian cells. Recombinant baculovirus-infected insect cell-derived Id showed higher binding to and activation of human dendritic cells mediated by **mannose receptors**. In vivo, insect cell-derived Id elicited higher levels of tumor-specific CD8(+) cytotoxic T lymphocyte (CTL) and improved eradication of pre-established murine lymphoma. Insect cell and mammalian Id generated similar levels of tumor-specific **antibodies**, showing no impairment in **antibody** responses to native tumor antigen despite the glycoslylation differences in the immunogen. Combining insect cell production and maleimide-based KLH conjugation offered the highest levels of anti-tumor immunity. Our data comparing sources of recombinant Id protein tumor antigens used in therapeutic cancer vaccines demonstrate that insect cell-derived antigens can offer several immunologic advantages over proteins derived from mammalian sources. .COPYRGT. 2008 Elsevier Ltd. All rights reserved.

L12 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2009 ACS on STN

2008:973996 Document No. 149:244360 Anti-DC-ASGPR **antibodies conjugated** with antigen for **targeting antigen-presenting cell** and enhancing antigen presentation against cancer and infection. Banchereau, Jacques F.; Oh, Sangkon; Zurawski, Gerard; Zurawski, Sandra; Li, Dapeng (Baylor Research Institute, USA). PCT Int. Appl. WO 2008097870 A2 20080814, 61pp. DESIGNATED STATES: W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, MT, NE, NL, NO, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2008-US52865 20080202. PRIORITY: US 2007-888036P

20070202.
AB The present invention includes compns. and methods for making and using DC-ASGPR or dendritic cell asialoglycoprotein receptor-specific **antibodies** or fragments that can, e.g., activate DCs and other cells.

L12 ANSWER 4 OF 8 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN DUPLICATE 1
2007265592 EMBASE **Antibody**-targeted vaccines.
Keler, T., Dr. (correspondence); He, L.; Ramakrishna, V.. Celldex Therapeutics, Inc., 222 Cameron Dr, Phillipsburg, NJ 08865, United States. tkeler@celldextherapeutics.com. Champion, B.. Celldex Therapeutics Ltd., Cambridge, United Kingdom.
Oncogene Vol. 26, No. 25, pp. 3758-3767 28 May 2007.
Refs: 84.
ISSN: 0950-9232. E-ISSN: 1476-5594. CODEN: ONCNES.
1210375. Pub. Country: United Kingdom. Language: English. Summary Language: English.
Entered STN: 20070621. Last Updated on STN: 20070621
AB The specificity and high affinity binding of **antibodies** provides these molecules with ideal properties for delivering a payload to target cells. This concept has been commercialized for cancer therapies using toxin- or radionucleotide-**conjugated antibodies** that are designed to selectively deliver cytotoxic molecules to cancer cells. Exploiting the same effective characteristics of **antibodies**, **antibody**-targeted vaccines (ATV) are designed to deliver disease-specific antigens to professional **antigen-presenting cells** (APCs), thus enabling the host's immune system to recognize and eliminate malignant or infected cells through adaptive immunity. The concept of ATVs has been in development for many years, and recently has entered clinical trials. Early studies with ATVs focused on the ability to induce humoral immunity in the absence of adjuvants. More recently, ATVs targeted to C-type lectin receptors have been exploited for induction of potent helper and cytolytic T-cell responses. To maximize their stimulatory capacity, the ATVs are being evaluated with a variety of adjuvants or other immunostimulatory agents. In the absence of co-administered immunostimulatory signals, APC-**targeting** can induce antigen-specific tolerance and, thus, may also be exploited in developing specific treatments for autoimmune and allergic diseases, or for preventing transplant rejection. The successful clinical application of this new class of **antibody**-based products will clearly depend on using appropriate combinations with other strategies that influence the immune system. .COPYRGT. 2007 Nature Publishing Group All rights reserved.

L12 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2009 ACS on STN
2005:824435 Document No. 143:246760 **Antibody** vaccine **conjugates** comprising antigen or tumor antigen linked to **antibody targeting antigen-presenting cells** for treating infectious and neoplastic diseases. Keler, Tibor; Endres, Michael; He, Lizhen; Ramakrishna, Venky (Celldex Therapeutics, Inc., USA). U.S. Pat. Appl. Publ. US 20050180983 A1 20050818, 48 pp., Cont.-in-part of U.S. Ser. No. 769,144. (English). CODEN: USXXCO. APPLICATION: US 2004-903191 20040730. PRIORITY: US 2003-443979P 20030131; US 2004-769144 20040130.
AB The present invention provides novel **antibody** vaccine **conjugates** and methods of using the same to induce a cytotoxic T cell (CTL) response. In a particular, embodiment, the vaccine **conjugate** includes a human chorionic gonadotropin β subunit (βhCG) antigen linked to an anti- **mannose receptor** (MR) **antibody**. The vaccine **conjugates** may also be tumor antigen, bacterial antigen, viral antigen, carbohydrate or fungal

protein. The **antibody** may also be anti-CD40 ligand, anti-cytokine, anti-CTLA-4, anti-toll receptor agonist, or other immunostimulatory agent such as R837, R848, polyI:C, ssRNA, dsRNA, BCG, Levamisole hydrochloride or i.v. Ig.

L12 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2009 ACS on STN
2004:1126838 Document No. 142:73405 Vaccines comprising anti-DEC-205 **antibody**-antigen **conjugates** with or without dendritic cell maturation factor for enhancing long lasting antigen presentation or inducing tolerance. Hawiger, Daniel; Nussenzweig, Michel; Steinman, Ralph M.; Bonifaz, Laura (USA). U.S. Pat. Appl. Publ. US 20040258688 A1 20041223, 116 pp., Cont.-in-part of U.S. Ser. No. 925,284. (English). CODEN: USXXCO. APPLICATION: US 2004-800023 20040312. PRIORITY: US 1995-381528 19950131; WO 1996-US1383 19960131; US 2000-586704 20000605; US 2001-925284 20010809.

AB The present invention relates to methods for **targeting** antigen to **antigen presenting cells** through specific endocytic receptors, which results in persistent antigen presentation in the context of MHC mols. Such highly efficient antigen presentation results in robust and long lasting immune responses, in particular cell mediated responses. The invention provides for immune compns. containing **antibodies** to DEC-205 in combination with the antigen for eliciting either T cell mediated immunity when delivered with a dendritic cell maturation factor, or for inducing tolerance when delivered in the absence of a dendritic cell maturation factor. The antigen is tumor antigen or pathogenic antigen; and the dendritic cell maturation factor is anti-CD4 **antibody**, inflammatory cytokine, polyI/C, single stranded RNA, DNA, CpG, ligation of IL-1, TNF or TOLL-like receptor, TRAF-6 or NF-κB. The compns. described in the present invention are effective as a single dose at low concns. and show efficacy even with non-replicating subunit vaccines.

L12 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2009 ACS on STN
2003:118018 Document No. 138:168835 **Targeting** of an **antigen presenting cell** (APC) with a modulator of T cell signalling, such as a Notch ligand, coupled to the MHC class II-binding motif from a superantigen. Bodmer, Mark William; Champion, Brian Robert; McKenzie, Grahame James; Nye, Lucy Emma (Lorantis Limited, UK). PCT Int. Appl. WO 2003012111 A2 20030213, 93 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-GB3381 20020725. PRIORITY: GB 2001-18155 20010725.

AB The present invention relates to the concept of delivering a modulator of T cell signaling, such as a Notch ligand, to an **antigen presenting cell** (APC). The **targeting** approach disclosed uses, for example, the major histocompatibility complex (MHC) class II binding motif from a superantigen coupled to a modulator of the Notch signaling pathway. Superantigens bind both MHC class II mols. and subsets of T cell receptors and thus effectively cross-link APCs to T cells and activate cells polyclonally. The mol. regions of these mols. that impart T cell receptor (TCR) and MHC class II binding have been defined structurally and have been shown to be distinct regions of the mol. By using the MHC class II binding domain with a modulator of the Notch signaling pathway we can focus the activity of the Notch signaling pathway modulator to the APCs at the site of delivery. Further, the domain lacks toxin activity because it cannot find the T cell receptor to

activate T cells. According to one aspect of the present invention there is provided a **conjugate** comprising a first and a second sequence wherein the first sequence comprises a polypeptide which is capable of binding to an APC, or a polynucleotide encoding therefor, and the second sequence comprises a polypeptide comprising a modulator of a signaling pathway in a T cell or a polynucleotide encoding therefor.

L12 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2009 ACS on STN
2001:833384 Document No. 135:370640 Human monoclonal **antibodies** to dendritic cells. Deo, Yashwant M.; Keler, Tibor (Medarex, Inc., USA). PCT Int. Appl. WO 2001085798 A2 20011115, 95 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US15114 20010508. PRIORITY: US 2000-203126P 20000508; US 2000-230739P 20000907.
AB Isolated human monoclonal **antibodies** and antigen-binding portions thereof which specifically bind to dendritic cells are disclosed. Also disclosed are bispecifics, immunotoxins and antigen **conjugates** which include the **antibodies** or **antibody** portions. The human **antibodies** can be produced in a non-human transgenic animal, e.g. a transgenic mouse, capable of producing multiple isotypes of human monoclonal **antibodies** by undergoing V-D-J recombination and isotype switching. Also disclosed are pharmaceutical compns. comprising the human **antibodies**, non-human transgenic animals and hybridomas which produce the human **antibodies**. The invention also provides therapeutic and diagnostic methods for autoimmune diseases or graft vs. host diseases by using the human **antibodies**.

=> s l2 and CD206
L13 4 L2 AND CD206

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L14 2 DUP REMOVE L13 (2 DUPLICATES REMOVED)

=> d l14 1-2 cbib abs

L14 ANSWER 1 OF 2 MEDLINE on STN DUPLICATE 1
2007621035. PubMed ID: 17947679. The novel endocytic and phagocytic C-Type lectin receptor DCL-1/CD302 on macrophages is colocalized with F-actin, suggesting a role in cell adhesion and migration. Kato Masato; Khan Seema; d'Aniello Elisabetta; McDonald Kylie J; Hart Derek N J. (Dendritic Cell Program, Mater Medical Research Institute, South Brisbane, Queensland, Australia.) Journal of immunology (Baltimore, Md. : 1950), (2007 Nov 1) Vol. 179, No. 9, pp. 6052-63. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.
AB C-type lectin receptors play important roles in mononuclear phagocytes, which link innate and adaptive immunity. In this study we describe characterization of the novel type I transmembrane C-type lectin DCL-1/CD302 at the molecular and cellular levels. DCL-1 protein was highly conserved among the human, mouse, and rat orthologs. The human DCL-1 (hDCl-1) gene, composed of six exons, was located in a cluster of type I transmembrane C-type lectin genes on chromosomal band 2q24. Multiple tissue expression array, RT-PCR, and FACS analysis using new anti-hDCL-1 mAbs established that DCL-1 expression in leukocytes was

restricted to monocytes, macrophages, granulocytes, and dendritic cells, although DCL-1 mRNA was present in many tissues. Stable hDCL-1 Chinese hamster ovary cell transfectants endocytosed FITC-**conjugated** anti-hDCL-1 mAb rapidly (t(1/2) = 20 min) and phagocytosed anti-hDCL-1 mAb-coated microbeads, indicating that DCL-1 may act as an Ag uptake receptor. However, anti-DCL-1 mAb-coated microbead binding and subsequent phagocytic uptake by macrophages was approximately 8-fold less efficient than that of anti-macrophage mannose receptor (MMR/**CD206**) or anti-DEC-205/CD205 mAb-coated microbeads. Confocal studies showed that DCL-1 colocalized with F-actin in filopodia, lamellipodia, and podosomes in macrophages and that this was unaffected by cytochalasin D, whereas the MMR/**CD206** and DEC-205/CD205 did not colocalize with F-actin. Furthermore, when transiently expressed in COS-1 cells, DCL-1-EGFP colocalized with F-actin at the cellular cortex and microvilli. These data suggest that hDCL-1 is an unconventional lectin receptor that plays roles not only in endocytosis/phagocytosis but also in cell adhesion and migration and thus may become a target for therapeutic manipulation.

L14 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2009 ACS on STN
2003:118018 Document No. 138:168835 Targeting of an antigen presenting cell (APC) with a modulator of T cell signalling, such as a Notch ligand, coupled to the MHC class II-binding motif from a superantigen. Bodmer, Mark William; Champion, Brian Robert; McKenzie, Grahame James; Nye, Lucy Emma (Lorantis Limited, UK). PCT Int. Appl. WO 2003012111 A2 20030213, 93 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-GB3381 20020725. PRIORITY: GB 2001-18155 20010725.
AB The present invention relates to the concept of delivering a modulator of T cell signaling, such as a Notch ligand, to an antigen presenting cell (APC). The targeting approach disclosed uses, for example, the major histocompatibility complex (MHC) class II binding motif from a superantigen coupled to a modulator of the Notch signaling pathway. Superantigens bind both MHC class II mols. and subsets of T cell receptors and thus effectively cross-link APCs to T cells and activate cells polyclonally. The mol. regions of these mols. that impart T cell receptor (TCR) and MHC class II binding have been defined structurally and have been shown to be distinct regions of the mol. By using the MHC class II binding domain with a modulator of the Notch signaling pathway we can focus the activity of the Notch signaling pathway modulator to the APCs at the site of delivery. Further, the domain lacks toxin activity because it cannot find the T cell receptor to activate T cells. According to one aspect of the present invention there is provided a **conjugate** comprising a first and a second sequence wherein the first sequence comprises a polypeptide which is capable of binding to an APC, or a polynucleotide encoding therefor, and the second sequence comprises a polypeptide comprising a modulator of a signaling pathway in a T cell or a polynucleotide encoding therefor.

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(FILE 'HOME' ENTERED AT 10:09:31 ON 11 AUG 2009)

FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 10:09:49 ON 11 AUG 2009
L1 601032 S CONJUGATE?

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L2       123941 S L1 AND ANTIBOD?
L3           87 S L2 AND MANNOSE RECEPTOR
L4            1 S L3 AND NOTCH LIGAND
L5            0 S L3 AND "HUMAN DELTA 1"
L6            0 S L3 AND "HUMAN DELTA 3"
L7            0 S L3 AND "HUMAN DELTA 4"
L8            0 S L3 AND "HUMAN JAGGED 1"
L9            0 S L3 AND "HUMAN JAGGED 2"
L10          21 S L3 AND TARGETING
L11           9 S L10 AND ANTIGEN PRESENTING CELL
L12           8 DUP REMOVE L11 (1 DUPLICATE REMOVED)
L13           4 S L2 AND CD206
L14           2 DUP REMOVE L13 (2 DUPLICATES REMOVED)

=> s l2 and MHC class II
L15        497 L2 AND MHC CLASS II

=> s l15 and targeting
L16         66 L15 AND TARGETING

=> s l16 and Notch ligand
L17          1 L16 AND NOTCH LIGAND

=> d l17 cbib abs

L17  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2009 ACS on STN
2003:118018   Document No. 138:168835  Targeting of an antigen
     presenting cell (APC) with a modulator of T cell signalling, such as a
     Notch ligand, coupled to the MHC class
     II-binding motif from a superantigen.  Bodmer, Mark William;
     Champion, Brian Robert; McKenzie, Grahame James; Nye, Lucy Emma (Lorantis
     Limited, UK).  PCT Int. Appl. WO 2003012111 A2 20030213, 93 pp.
     DESIGNATED STATES: W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ,
     CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE,
     GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
     LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO,
     RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN,
     YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES,
     FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG,
     TR.  (English).  CODEN: PIXXD2.  APPLICATION: WO 2002-GB3381 20020725.
     PRIORITY: GB 2001-18155 20010725.
AB   The present invention relates to the concept of delivering a modulator of
     T cell signaling, such as a Notch ligand, to an
     antigen presenting cell (APC).  The targeting approach disclosed
     uses, for example, the major histocompatibility complex (MHC)
     class II binding motif from a superantigen coupled to a
     modulator of the Notch signaling pathway.  Superantigens bind both
     MHC class II mols. and subsets of T cell
     receptors and thus effectively cross-link APCs to T cells and activate
     cells polyclonally.  The mol. regions of these mols. that impart T cell
     receptor (TCR) and MHC class II binding have
     been defined structurally and have been shown to be distinct regions of
     the mol.  By using the MHC class II binding
     domain with a modulator of the Notch signaling pathway we can focus the
     activity of the Notch signaling pathway modulator to the APCs at the site
     of delivery.  Further, the domain lacks toxin activity because it cannot
     find the T cell receptor to activate T cells.  According to one aspect of
     the present invention there is provided a conjugate comprising a
     first and a second sequence wherein the first sequence comprises a
     polypeptide which is capable of binding to an APC, or a polynucleotide
     encoding therefor, and the second sequence comprises a polypeptide
     comprising a modulator of a signaling pathway in a T cell or a
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polynucleotide encoding therefor.

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L18 31 DUP REMOVE L16 (35 DUPLICATES REMOVED)

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L19 21 L18 AND PD<19990504

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L20 ANSWER 1 OF 21 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
1999102071 EMBASE A novel immunization method to induce cytotoxic T-lymphocyte responses (CTL) against plasmid-encoded herpes simplex virus type-1 glycoprotein D.
Cruz, P.E.; Khalil, P.L.; Dryden, T.D.; Fink, P.S.; Bigley, N.J. (correspondence). Depts. of Microbiol. and Immunology, Wright Stt. Univ., 3640 Col. G., Dayton, OH 45435, United States. nbigley@desire.wright.edu. Chiou, H.C.. The Immune Response Corporation, Carlsbad, CA 92008, United States. Berberich, S.J.. Biochemistry and Molecular Biology, Wright State University, Dayton, OH 45435, United States. Bigley, N.J. (correspondence). Dept. of Microbiology and Immunology, Wright State University, 3640 Col. Glenn Highway, Dayton, OH 45435, United States. nbigley@desire.wright.edu.
Vaccine Vol. 17, No. 9-10, pp. 1091-1099 **5 Mar 1999.**
Refs: 28.
ISSN: 0264-410X. CODEN: VACCDE.
S 0264-410X(98)00326-0. Pub. Country: United Kingdom. Language: English. Summary Language: English.
Entered STN: 19990419. Last Updated on STN: 19990419
AB DNA molecules complexed with an asialoglycoprotein-polycation **conjugate**, consisting of asialoorosomucoid (ASOR) coupled to poly-L-lysine, can enter hepatocytes which bear receptors for ASOR. We used this receptor-mediated DNA delivery system to deliver plasmid DNA encoding glycoprotein D (gD) of herpes simplex virus type 1 to ASOR-positive cells. Maximum expression of gD protein was seen at 3 days after injection of this preparation in approximately 13% of cells from BALB/c mice [hepatocytes from mice injected intravenously (i.v.) or peritoneal exudate cells from mice injected intraperitoneally (i.p.)]. In comparison with mice injected with either the plasmid vector alone or the gD-containing plasmid uncomplexed to ASOR, mice immunized with gD-containing plasmid complexed with ASOR-poly-L-lysine induced marked antigen-specific CTL responses. BALB/c mice immunized with gD-DNA developed a T-cell-mediated CTL response against target cells expressing gD and **MHC class II** glycoproteins, but not against cells expressing only gD and MHC class I molecules. In C3H mice, gD-DNA induced a T-cell-mediated CTL response against target cells expressing gD and class I MHC molecules. Serum anti-gD **antibody** in low titers were produced in both strains of mice. DNA complexed with ASOR- poly-L-lysine induced CTL responses in mice.

L20 ANSWER 2 OF 21 MEDLINE on STN
1998414403. PubMed ID: 9743446. **Targeting** of human and mouse T-lymphocytes by monoclonal **antibody**-HPMA copolymer-doxorubicin **conjugates** directed against different T-cell surface antigens.

Jelinkova M; Strohalm J; Plocova D; Subr V; St'astny M; Ulbrich K; Rihova B. (Institute of Microbiology, AS CR, Prague, Czech Republic.) Journal of controlled release : official journal of the Controlled Release Society, **(1998 Mar 31)** Vol. 52, No. 3, pp. 253-70. Journal code: 8607908. ISSN: 0168-3659. Pub. country: Netherlands. Language: English.

AB Binding of HPMA copolymer-**conjugated** doxorubicin targeted with monoclonal **antibodies** directed against various T-cell surface receptors, i.e. Thy1.2 (CDw90), I-A (**MHC class II**. glycoprotein), L3T4 (CD4), IL-2R (CD25) and CD3, is considerably increased in Con A stimulated T-lymphocytes. FACS analysis showed that the binding is most intensive with anti-Thy1.2 and anti-L3T4 targeted derivatives and it is proportional to the antiproliferative effect of the **antibody**-targeted drug. No binding and no antiproliferative capacity was observed after in vitro incubation of mouse T-cells with a nonspecific mouse IgG-HPMA-DOX **conjugate.** [3H]-TdR incorporation was inhibited considerably more in Con A stimulated T-cell culture and in EL4 mouse T-cell lymphoma as compared with the culture of nonactivated T-lymphocytes. This proves that intensively proliferating cells are more susceptible to the inhibitory action of an **antibody**-targeted drug. The cytotoxic efficacy of HPMA copolymer with GlyPheLeuGly or GlyLeuPheGly side-chains to which the drug is **conjugated** was superior to HPMA copolymer with GlyPheGly or GlyLeuGly side-chains. However, there is no direct correlation between the rate of in vitro drug release and the in vitro cytotoxicity of the respective **conjugates.** This suggests that the rate of drug release from the **conjugate** is only one factor responsible for the pharmacological efficacy of the preparation. Furthermore, we detected substantial and prolonged inhibition of proliferation of Con A activated T-cells only if doxorubicin was injected in vivo in the form of an anti-Thy1.2-targeted **conjugate.**

L20 ANSWER 3 OF 21 CAPLUS COPYRIGHT 2009 ACS on STN

1997:679116 Document No. 127:330381 Original Reference No. 127:64893a,64896a Modified/chimeric superantigens and their use. Antonsson, Per; Hansson, Johan; Bjork, Per; Dohlsten, Mikael; Kalland, Terje; Abrahmsen, Lars; Forsberg, Goran (Pharmacia & Upjohn AB, Swed.; Antonsson, Per; Hansson, Johan; Bjork, Per; Dohlsten, Mikael; Kalland, Terje; Abrahmsen, Lars; Forsberg, Goran). PCT Int. Appl. WO 9736932 A1 **19971009**, 58 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-SE537 19970326. PRIORITY: SE 1996-1245 19960329; US 1996-695692 19960812.

AB A **conjugate** between a target-seeking moiety and a modified superantigen, characterized in that the superantigen is a wild-type superantigen (SA I) in which an amino acid residue in a superantigen region (region I) determining binding to TCR, preferably TCR Vβ, and T cell activation have been replaced by another amino acid residue while retaining the ability to activate a subset of T cells. In a preferred embodiment the modified superantigen is a chimer between at least two wild-type superantigens (SA I, SA II etc.) characterized in that one or more amino acid residues in a region determining binding to TCR and T cell activation have been interchanged between various wild-type superantigens. A therapeutic method making use of modified/chimeric superantigens as defined in the preceding paragraphs. An **antibody** preparation in which the cysteine residues that provide for interchain disulfide bonds have been mutated so as to forbid interchain disulfide bridges, preferably to serine residues, for use as a pharmaceutical. Plasmid 5T4Fab-SEA encoding fusion protein containing **antibody** 5T4 variable region and

murine IgG1 Vκ chain and Staphylococcal enterotoxin A was constructed, and the expressed chimeric superantigen was tested.

L20 ANSWER 4 OF 21 MEDLINE on STN

1997300616. PubMed ID: 9155636. Intranasal antigen **targeting** to **MHC class II** molecules primes local IgA and serum IgG **antibody** responses in mice. Snider D P; Underdown B J; McDermott M R. (Department of Pathology, McMaster University, Hamilton, Ontario, Canada.) Immunology, **(1997 Mar)** Vol. 90, No. 3, pp. 323-9. Journal code: 0374672. ISSN: 0019-2805. Report No.: NLM-PMC1456616. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Covalent **conjugates** of hen egg lysozyme (HEL) and anti-major histocompatibility complex (**MHC**) **class II** monoclonal **antibodies** (mAb) were used to immunize mice intranasally. Three weeks after intranasal (IN) priming, mice responded rapidly to IN challenge with a mixture of HEL and cholera toxin (CT), by producing large titres of anti-HEL IgA and IgG1 **antibody** in serum, and IgA **antibody** in nasal secretions. No secondary response to HEL plus CT occurred in mice that received no priming or mice primed with HEL alone. The secondary serum IgG **antibody** response was dominated by the IgG1 subclass. HEL combined with CT adjuvant worked much better than HEL alone in producing the secondary response. Control **conjugates**, containing an IgG isotype-matched mAb without specificity for mouse tissues, provided poor priming. Mice expressing **MHC class II** molecules, to which the anti-MHC II mAb could not bind, produced a weak **antibody** response compared with those that expressed the appropriate. **MHC class II** molecule. Our results demonstrate that immunotargeting to **MHC class II** molecules via the IN route allows priming of the local IgA and circulating IgG **antibody**, and indicate that this technique is a feasible approach for delivery of subunit vaccines in the upper respiratory tract.

L20 ANSWER 5 OF 21 MEDLINE on STN

1997389629. PubMed ID: 9246765. Morphology of rat kidney and thymus after native and **antibody**-coupled cyclosporin A application (reduced toxicity of targeted drug). Rossmann P; Rihova B; Strohalm J; Ulbrich K. (Institute of Microbiology, Academy of Sciences of the Czech Republic, Prague.) Folia microbiologica, **(1997)** Vol. 42, No. 3, pp. 277-87. Journal code: 0376757. ISSN: 0015-5632. Pub. country: Czech Republic. Language: English.

AB This study compares the toxic effects of native cyclosporia A (CyA) with those of targeted CyA that is **conjugated** with the anti-rat-thymocyte **antibody** of rabbit origin via the N-(2-hydroxypropyl)methacrylamide (HPMA) carrier bearing digestible, reactive oligopeptide side chains. Ten toxic doses of native CyA (50 mg/kg i.p.) given to young adult rats in the course of 14 d produced a severe renal lesion-diffuse microvacuolization of the proximal tubules in the deep cortex, and hypergranulation of juxtaglomerular regions. Severe atrophy of the thymic medulla was documented by morphometry. In the cortex the epithelial reticular (but not deep interdigitating) cells showed ultrastructural signs of severe degeneration and lysis. The immature CD4+8+ double-positive cortical lymphocytes were preserved whereas the single-positive medullary thymocytes were greatly depleted; there was also a restriction of **MHC class II** antigen expression in the medulla. The number of medullary B cells was increased. The cytokeratin net was focally shrunken in the cortex and almost negative in the medulla, with loss of Hassall's corpuscles. After ten corresponding doses of **antibody**-targeted **conjugated** CyA no damage to the renal tubules and arterioles appeared and the antiGBM or immune-complex deposition was absent. The thymus had a normal medulla

with numerous mature thymocytes and the cortical epithelial reticulum remained well preserved. Thus, the main toxic effects of CyA could be eliminated by **targeting**. The T-cell-targeted drug was tested for preserved immunosuppressive properties and non-toxic character of HPMA copolymer carrier.

L20 ANSWER 6 OF 21 MEDLINE on STN
1997339000. PubMed ID: 9195560. Superantigen-induced lysis of melanoma cells. Krull F; Holzer U; Ihle J; Bethge W; Fierlbeck G; Kalland T; Dohlsten M; Niethammer D; Dannecker G E. (Department of Oncology and Hematology, Children's University Hospital, Tubingen, Germany.) Melanoma research, **(1997 Jun)** Vol. 7, No. 3, pp. 214-22. Journal code: 9109623. ISSN: 0960-8931. Pub. country: ENGLAND: United Kingdom. Language: English.
AB Superantigens like the Staphylococcus enterotoxin A (SEA) can direct cytotoxic T lymphocytes expressing certain T cell receptor V beta regions to lyse **MHC class II**-positive target cells. This superantigen-dependent cellular cytotoxicity (SDCC) has been extended to **MHC class II**-negative tumour cells by **targeting** T cells via **conjugates** of a tumour-specific monoclonal **antibody** (moAb) and a superantigen. In the present study the **MHC class II**-negative human melanoma cell lines G361 and MaRI were tested for susceptibility to SDCC in vitro. **Antibodies** recognizing the disialoganglioside GD3 and the CD10 antigen were linked to SEA either by a recombinant protein A-SEA fusion protein or an anti-kappa moAb-SEA chemical **conjugate.** Specific lysis of melanoma cells was dose- and effector to target (E:T) cell ratio-dependent. Introduction of a point mutation into the SEA gene (producing SEAm9) in order to reduce MHC II affinity of the superantigen, which has already been shown to severely diminish superantigen-dependent binding and lysis of **MHC class II**-positive cells, did not influence **antibody**-targeted SDCC. Cytotoxicity was equal with both **antibodies** (anti-GD3 and anti-CD10) and independent of whether protein A-SEA, protein A-SEAm9 or anti-kappa-SEA were used.

L20 ANSWER 7 OF 21 CAPLUS COPYRIGHT 2009 ACS on STN
1996:254276 Document No. 124:340904 Original Reference No. 124:63325a
Methods and bifunctional ligands for specific tumor inhibition by blood coagulation in tumor vasculature. Thorpe, Philip E.; Edgington, Thomas S. (Univ. of Texas System, USA; Scripps Res. Inst.). PCT Int. Appl. WO 9601653 A1 **19960125**, 325 pp. DESIGNATED STATES: W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TT, UA; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1995-US7439 19950607. PRIORITY: US 1994-273567 19940711.
AB Bispecific binding ligands are provided which bind through a 1st binding region to a disease-related target cell, e.g. a tumor cell or tumor vasculature; the 2nd region has coagulation-promoting activity or is a binding region for a coagulation factor. Since tumor vasculature is prothrombotic and is predisposed towards coagulation, these targeted coagulants selectively induce blood coagulation in vessels supplying the tumor and cause death of tumor cells. The bispecific binding ligand may be a bispecific (monoclonal) **antibody**, or the 2 ligands may be connected by a (selectively cleavable) covalent bond, a chemical linking agent, an avidin-biotin linkage, etc. The target of the 1st binding region may be a cytokine-inducible component, and cytokine may be release in response to a leukocyte-activating **antibody**; this may be a bispecific **antibody** which crosslinks activated leukocytes with tumor cells. Alternatively, the target of the 1st binding region may be a

component (e.g. E- or P-selectin) which is inducible by thrombin, where thrombin production is induced by administration of a bispecific **antibody** which binds to a tumor cell and to tissue factor, prothrombin, factor VII/VIIa, factor IX/IXa, etc. Thus, a coaguligand (bispecific **antibody** capable of **targeting** a coagulant to a tumor site) was prepared by chemical coupling an Fab' fragment from monoclonal **antibody** B21-2 (which reacts with I-Ad antigen expressed on A20 B-cell lymphoma cells and on the vasculature of C1300 transfectant mouse tumors) with an Fab' fragment from monoclonal **antibody** 10H10 (which reacts with human tissue factor). Incubation of A20 cells with this bispecific **antibody** and recombinant human truncated tissue factor resulted in tethering of tissue factor to the cells; plasma added to the A20 cell-tissue factor complex coagulated rapidly. Kits comprising the bifunctional ligand, a 2nd ligand, and optionally a drug for conjunctive therapy are described.

L20 ANSWER 8 OF 21 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN

1995321063 EMBASE Adjuvants for human vaccines. Current status, problems and future prospects.

Gupta, R.K. (correspondence); Siber, G.R.. MA Public Health Biologic Labs., State Laboratory Institute, Boston, MA 02130, United States.

Vaccine Vol. 13, No. 14, pp. 1263-1276 **1995.**

ISSN: 0264-410X. CODEN: VACCDE.

Pub. Country: United Kingdom. Language: English. Summary Language: English.

Entered STN: 951128. Last Updated on STN: 951128

AB Adjuvants help antigen to elicit an early, high and long-lasting immune response with less antigen, thus saving on vaccine production, costs. In recent years, adjuvants received much attention because of the development of purified, subunit and synthetic vaccines which are poor immunogens and require adjuvants to evoke the immune response. With the use of adjuvants immune response can be selectively modulated to major histocompatibility complex (MHC) class I or **MHC class II** and Th1 or Th2 type, which is very important for protection against diseases caused by intracellular pathogens such as viruses, parasites and bacteria (Mycobacterium). A number of problems are encountered in the development and use of adjuvants for human vaccines. The biggest issue with the use of adjuvants for human vaccines, particularly routine childhood vaccines is the toxicity and adverse side-effects of most of the adjuvant formulations. At present the choice of adjuvants for human vaccination reflects a compromise between a requirement for adjuvanticity and an acceptable low level of side-effects. Other problems with the development of adjuvants include restricted adjuvanticity of certain formulations to a few antigens, use of aluminum adjuvants as reference adjuvant preparations under suboptimal conditions, non-availability of reliable animal models, use of non-standard assays and biological differences between animal models and humans leading to the failure of promising formulations to show adjuvanticity in clinical trials. The most common adjuvants for human use today are still aluminum hydroxide and aluminum phosphate, although calcium phosphate and oil emulsions also have some use in human vaccinations. During the last 15 years much progress has been made on development, isolation and chemical synthesis of alternative adjuvants such as derivatives of muramyl dipeptide, monophosphoryl lipid A, liposomes, QS21, MF-59 and immunostimulating complexes (ISCOMS). Other areas in adjuvant research which have received much attention are the controlled release of vaccine antigens using biodegradable polymer microspheres and reciprocal enhanced immunogenicity of protein-polysaccharide **conjugates.** Biodegradable polymer microspheres are being evaluated for **targeting** antigens on mucosal surfaces and for controlled release of vaccines with an aim to reduce the number of doses required for primary immunization. Reciprocal

enhanced immunogenicity of protein-polysaccharide **conjugates** will be useful for the development of combination vaccines.

L20 ANSWER 9 OF 21 MEDLINE on STN

1996021574. PubMed ID: 7483762. Intestinal immunization of mice with antigen **conjugated** to anti-**MHC class II antibodies**. Estrada A; McDermott M R; Underdown B J; Snider D P. (Department of Pathology, McMaster University, Hamilton, Ontario, Canada.) Vaccine, **(1995 Jul)** Vol. 13, No. 10, pp. 901-7. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB We have explored a new technique for immunization of the intestinal tract of mice, using protein antigens bound to **antibodies** with specificity for murine **MHC class II** molecules (MHC-II). Either of two protein antigens, hen avidin (AV) or hen egg lysozyme (HEL) were covalently **conjugated** to anti-MHC-II **antibodies** and the purified **conjugates** were given orally (p.o.) or by direct intraduodenal (i.d.) injection into the intestinal lumen of mice. A secondary immunization p.o. with the same **conjugate** or with the non-**conjugated** antigen in the presence of cholera toxin (CTX) resulted in production of both intestinal secretory IgA and serum IgA **antibody** by those mice. In addition, serum IgG **antibodies** were produced. **Conjugates** with appropriate MHC-II specificity targeted the antigen because they induced more IgA and IgG **antibody** than **conjugates** with irrelevant **antibody** specificity or antigen alone, and because they induced **antibody** in mice that were genetic low responders to antigen. The results indicate the feasibility of oral subunit type vaccines with **antibody targeting** technology.

L20 ANSWER 10 OF 21 MEDLINE on STN

1995136241. PubMed ID: 7530598. **Antibody**-targeted superantigens induce lysis of major histocompatibility complex class II-negative T-cell leukemia lines. Ihle J; Holzer U; Krull F; Dohlsten M; Kalland T; Niethammer D; Dannecker G E. (Department of Oncology/Hematology, Children's University Hospital, Tubingen, Germany.) Cancer research, **(1995 Feb 1)** Vol. 55, No. 3, pp. 623-8. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB CTLs bearing certain T-cell receptor V beta-regions are directed by the bacterial superantigen Staphylococcus enterotoxin A (SEA) to lyse **MHC class II**-positive cells. In order to extend superantigen-dependent cytotoxicity to **MHC class II**-negative carcinoma cells, covalent **conjugates** of superantigen and mAbs against surface markers of these cells have been used. We now describe a novel strategy which allows rapid selection of mAb suitable for superantigen **targeting** against **MHC class II**-negative tumor cells. A recombinant fusion protein of protein A and SEA binding to the mAbs CD7 or CD38 was able to mediate T cell-dependent lysis of **MHC class II** -negative Molt-4 and CCRF-CEM acute lymphatic leukemia cell lines. Lysis was dose dependent and correlated with E:T cell ratio. In contrast, SEA alone did not induce any significant lysis. In order to decrease the **MHC class II** affinity of the protein A-SEA complex, a point mutation was introduced into SEA (protein A-SEA mu9). The mutated fusion protein had similar potency as protein A-SEA against Molt-4 cells but was 100-fold less active against **MHC class II**-positive cells. Considering the efficiency and specificity of the mutated SEA protein interacting with mAb in **targeting** T lymphocytes against **MHC class II**-negative leukemia cells while only marginally affecting normal **MHC class II**-positive cells, we suggest the

development of SEA-mAb fusion proteins as a potential adjuvant therapy of leukemias.

L20 ANSWER 11 OF 21 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN
1995:206745 Document No.: PREV199598221045. Dendritic leucocytes pulsed with monoclonal **antibody**-hapten **conjugates** elicit vigorous primary humoral responses in vivo. Mjaaland, Siri [Reprint author]; Fossum, S.. Dep. Virol., Central Vet. Lab., Pb. 8156 Dep., N-0033 Oslo, Norway. Scandinavian Journal of Immunology, (**1995**) Vol. 41, No. 3, pp. 305-308.
CODEN: SJIMAX. ISSN: 0300-9475. Language: English.
AB Purified dendritic leukocytes (DL) were pulsed briefly in vitro with haptenated monoclonal **antibodies** (MoAb) to **MHC class II** and immediately injected i.v. into syngeneic recipients. Strong anti-hapten humoral responses were observed even though only a few picomoles of specific MoAb-hapten **conjugates** were injected with the DL. In contrast, DL pulsed with control **conjugates**, i.e. haptenated non-binding MoAbs, gave only weak responses. DL thus, can take up, process and present protein antigens even after brief exposure in vitro, and their immunogenicity is enhanced by pulsing with antigen **conjugated** to specific MoAbs. Furthermore, in the presence of fetal calf serum (FCS), but not normal rat serum, the control MoAb W6/32 (against human MHC class I) bound to DL. The vigorous primary humoral response achieved following this pulsing indicates that it is the binding and the corresponding increased uptake that enhances the immunogenicity of the DL.

L20 ANSWER 12 OF 21 MEDLINE on STN
1994265813. PubMed ID: 8206087. Comparing macrophages and dendritic leukocytes as antigen-presenting cells for humoral responses in vivo by antigen **targeting**. Berg S F; Mjaaland S; Fossum S. (Institute of Basic Medical Sciences, University of Oslo, Norway.) European journal of immunology, **(1994 Jun)** Vol. 24, No. 6, pp. 1262-8. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.
AB Immunotargeting is a novel technique whereby antigen is directed against antigen-presenting cells (APC) by conjugation to specific monoclonal **antibodies** (mAb). In this study we have employed the technique to investigate the efficiency of macrophages as APC compared with constitutively major histocompatibility complex (**MHC**) **class II**-positive cells, i.e. dendritic leukocytes and B cells, in vivo. We first studied the organ retention of the radiolabeled **conjugates** by gamma counting, and their distribution within the draining lymph nodes by autoradiography. We could confirm that the **conjugates** reached the cells at which they were aimed. We then measured primary and secondary humoral responses. The results confirmed previous findings that **targeting** with mAb against **MHC class II**, i.e. to dendritic leukocytes, strongly enhanced the primary humoral response. In contrast, anti-IgD **conjugates**, directed against B cells gave only weak primary responses. Although **conjugates** directed against macrophages were retained for a longer time than the other **conjugates**, the primary humoral response was virtually abolished. The secondary responses, however, were at least as strong as those obtained in animals primed with control **conjugates**, whereas animals primed with anti-**MHC class II conjugates** showed little if any amplification of the secondary response. The discrepancies between the various **conjugates** could not be ascribed to TH1 versus TH2 responses as IgG1, IgG2a, IgG2b and IgE titers all co-varied in single animals. A possible explanation for the observed results is that macrophages fail to induce cytokine production for

terminal differentiation of B cells to plasma cells, whereas conversely, upon presentation by dendritic leukocytes most stimulated B cells mature to plasma cells, leaving less progeny for immunological memory.

L20 ANSWER 13 OF 21 CAPLUS COPYRIGHT 2009 ACS on STN
1993:656537 Document No. 119:256537 Original Reference No. 119:45649a,45652a
Diagnostic and/or therapeutic immunoconjugates targeted to neovascular endothelial cells. Thorpe, Philip E.; Burrows, Francis J. (University of Texas System, USA; Imperial Cancer Research Technology Ltd.). PCT Int. Appl. WO 9317715 A1 **19930916**, 171 pp. DESIGNATED STATES: W: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1993-US1956 19930305. PRIORITY: US 1992-846349 19920305.
AB An **antibody** or **antibody** fragment that recognizes a cell surface antigen associated with endothelial vasculature of a vascularized tumor mass is linked to a therapeutic or diagnostic agent for treatment or diagnosis of vascularized tumors. The **antibody** may be linked to a paramagnetic or radioactive ion, cytotoxic agent, cytokine, etc. Thus, a neuroblastoma transfected with the mouse γ-interferon gene was grown in mice with severe combined immunodeficiency. The γ-interferon secreted by the tumor induced expression of **MHC class II** antigens on the tumor vascular endothelium. A rat IgG2b monoclonal **antibody** which recognized MHC Ia antigens, **conjugated** to deglycosylated ricin A chain, was used successfully for treatment of the neuroblastoma.

L20 ANSWER 14 OF 21 CAPLUS COPYRIGHT 2009 ACS on STN
1993:641036 Document No. 119:241036 Original Reference No. 119:42691a,42694a
Eradication of large solid tumors in mice with an immunotoxin directed against tumor vasculature. Burrows, Francis J.; Thorpe, Philip E. (Southwest. Med. Cent., Univ. Texas, Dallas, TX, 75235-8576, USA). Proceedings of the National Academy of Sciences of the United States of America, 90(19), 8996-9000 (English) **1993**. CODEN: PNASA6. ISSN: 0027-8424.
AB **Antibody**-based therapy of solid tumors has met with limited success, chiefly because solid tumors are relatively impermeable to macromols. This problem could be circumvented by attacking the readily accessible endothelial cells of the tumor vascular bed. The authors have developed a model to test this "vascular **targeting**" approach in which cytokine gene transfection of the tumor cells causes them to induce an exptl. marker selectively on tumor vascular endothelium. An antitumor endothelial cell immunotoxin caused complete occlusion of the tumor vasculature and dramatic regressions of large solid tumors. By contrast, a conventional antitumor cell immunotoxin of equivalent in vitro potency produced only minor, transient antitumor effects but, when combined, the two immunotoxins induced permanent complete remissions in over half of the animals. These expts. indicate that immunotoxins directed against recently described markers on vascular endothelial cells in human tumors could provide a general treatment for solid tumors in humans.

L20 ANSWER 15 OF 21 CAPLUS COPYRIGHT 2009 ACS on STN
1993:557862 Document No. 119:157862 Original Reference No. 119:28249a,28252a
Acetylcholine receptor presentation by B cells using heterobifunctional **antibody conjugates**. Reim, Johannes; McIntosh, Kevin R.; Drachman, Daniel (Sch. Med., Johns Hopkins Univ., Baltimore, MD, 21205, USA). Annals of the New York Academy of Sciences, 681(Myasthenia Gravis and Related Disorders: Experimental and Clinical Aspects), 325-8 (English) **1993**. CODEN: ANYAA9. ISSN: 0077-8923.
AB Helper T cells recognize processed peptides derived from antigens, presented in association with self-**MHC class II**

antigens. B cells serve as potent antigen-presenting cells (APC) when antigen is target to B-cell surface structures. The authors have targeted acetylcholine receptor (AChR) to surface Ig (sIg) using heterobifunctinal **conjugates** consisting of **antibodies** directed against B-cell sIg and monoclonal **antibody** directed against AChR. In this study,the authors assessed the effectiveness of **conjugate** plus AChR-treated B cells (AChR-APC) in **targeting** AChR-specific T-cells. Time-course expts. were performed to assess the difference in time of AChR uptake, processing, and presentation by B-cell prepns. treated with **conjugate** followed by AChR, as compared with control cells treated with AChR alone. There was a marked acceleration of these processes by the former cell prepns., as compared to the latter.

L20 ANSWER 16 OF 21 MEDLINE on STN
1995196232. PubMed ID: 7889537. **Targeting** of superantigens. Kalland T; Dohlsten M; Abrahmsen L; Hedlund G; Bjork P; Lando P A; Sundstedt A; Akerblom E; Lind P. (Kabi Pharmacia Oncology, Lund, Sweden.) Cell biophysics, **(1993 Jan-Jun)** Vol. 22, No. 1-3, pp. 147-64. Ref: 34. Journal code: 8002185. ISSN: 0163-4992. Pub. country: United States. Language: English.

AB The bacterial superantigen staphylococcal enterotoxin A (SEA) is an extremely potent activator of T lymphocytes when presented on **MHC class II** antigens. In order to induce T lymphocytes to reject a tumor, we substituted the specificity of SEA for **MHC class II** molecules with specificity for tumor cells by combining SEA with a MAb recognizing colon carcinomas. Chemical **conjugates** or recombinant fusion proteins of the MAb C215 and SEA retained excellent antigen binding properties whereas the binding to **MHC class II** was markedly reduced. The hybrid proteins directed SEA responsive T cells to tumors with specificity determined by the specificity of the MAb. Significant tumor cell killing was obtained at picomolar concentrations of the hybrid proteins and was the result of direct cell mediated by cytotoxicity as well as production of tumoricidal cytokines by T cells. **Targeting** of superantigens represents a novel approach to specific immunomodulation and deserves further study as a potential therapy for malignant disease.

L20 ANSWER 17 OF 21 MEDLINE on STN
1992021035. PubMed ID: 1924393. Monoclonal **antibody**-targeted superantigens: a different class of anti-tumor agents. Dohlsten M; Hedlund G; Akerblom E; Lando P A; Kalland T. (Kabi Pharmacia Therapeutics AB, Lund, Sweden.) Proceedings of the National Academy of Sciences of the United States of America, **(1991 Oct 15)** Vol. 88, No. 20, pp. 9287-91. Journal code: 7505876. ISSN: 0027-8424. Report No.: NLM-PMC52699. Pub. country: United States. Language: English.

AB The bacterial superantigen staphylococcal enterotoxin (SE) A (SEA) directs cytotoxic T lymphocytes (CTLs) expressing particular sequences of the T-cell receptor (TCR) beta chain to lyse tumor cells expressing major histocompatibility complex (**MHC**) **class II** molecules, which serve as receptors for SEs. We now report that chemical **conjugates** of SEA and the colon carcinoma-reactive monoclonal **antibodies** (mAbs) C215 or C242 mediate T cell-dependent destruction of colon carcinoma cells lacking **MHC class II** molecules. SEA was covalently linked to the mAbs C215 and C242 via a PEG-based hydrophilic spacer. The C215-SEA **conjugate** targeted CD4+ as well as CD8+ CTLs to lyse a panel of colon carcinoma cells lacking **MHC class II** molecules.
T-cell recognition of mAb-SEA **conjugates** was SEA specific, since SEB-selective T-cell lines with potent cytotoxic activity towards Raji cells coated with SEB did not respond to the C215-SEA **conjugate**. Unconjugated SEA did not induce T-cell lysis of **MHC class II**- colon carcinoma cells but efficiently directed

CTLs against **MHC class II**+ Raji cells and certain interferon-treated **MHC class II**+ colon carcinoma cells. These results suggest that SEA-mAb **conjugates** retain the SEA-related selectivity for certain TCR beta-chain variable region (V beta) sequences but, in contrast to unconjugated SEA, mediate the TCR interaction in a **MHC class II**-independent manner. The cytotoxic activity mediated by C215-SEA and C242-SEA **conjugates** was blocked by excess of C215 mAb and C242 mAb, respectively, showing that the specificity in the **targeting** of mAb-SEA **conjugates** is defined by the antigen reactivity of the mAb. These results demonstrate that bacterial superantigens may be successfully **conjugated** to mAb with preserved T cell-activating capacity. The circumvention of **MHC class II** binding of SEs by conjugation to mAb suggests that such **conjugates** may find general application as antitumor agents, taking advantage of the extreme T cell-activating potency of superantigens.

L20 ANSWER 18 OF 21 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN

1992:7057 The Genuine Article (R) Number: GV851. ANTIGEN **TARGETING** WITH MONOCLONAL-**ANTIBODIES** AS VECTORS .2. FURTHER EVIDENCE THAT CONJUGATION OF ANTIGEN TO SPECIFIC MONOCLONAL-**ANTIBODIES** ENHANCES UPTAKE BY ANTIGEN PRESENTING CELLS.
MJAALAND S (Reprint). UNIV OSLO, INST BASIC MED SCI, DEPT ANAT, IMMUNOBIOL LAB, POSTBOX 1105, N-0317 BLINDERN, NORWAY (Reprint). FOSSUM S.
INTERNATIONAL IMMUNOLOGY (**DEC 1991**) Vol. 3, No. 12, pp. 1315-1321. ISSN: 0953-8178. Publisher: OXFORD UNIV PRESS UNITED KINGDOM, WALTON ST JOURNALS DEPT, OXFORD, ENGLAND OX2 6DP. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Immunization of rats with haptenized monoclonal **antibodies** (mAbs) against accessory cells enhances anti-hapten **antibody** responses. To see whether the mAb-**conjugates** really targetted the antigen (hapten) to the antigen presenting cells, we have investigated the lymph node distribution of locally injected radiolabelled **conjugates**. Compared with control **conjugates**, i.e. haptenized non-binding mAbs, a much larger proportion of the specific **conjugates** were retained in the draining lymph nodes. Whereas control **conjugates** were rapidly phagocytosed and degraded by macrophages, the specific **conjugates** were associated with the targetted accessory cells, which were radiolabelled for extended periods. Haptenated MRC OX6 (anti-**MHC class II**) gave strong labelling of interdigitating cells (IDC) in the paracortex with 70% of IDC still labelled by 4 days and 15% by 16 days following injection. By Western blots intact OX6 **conjugates** were still detected in the draining lymph node as long as 3 days after injections, whereas control **conjugates** were hardly detectable even by 24 h. The findings substantiate the idea that mAbs can be exploited for vectorial transport of antigens to accessory cells.

L20 ANSWER 19 OF 21 MEDLINE on STN

1989235235. PubMed ID: 2523940. The **targeting** of CD4+ T lymphocytes to a B cell lymphoma. A comparison of anti-CD3-anti-idiotype **antibody conjugates** and antigen-anti-idiotype **antibody conjugates**. Gravelle M; Ochi A. (Division of Molecular Immunology and Neurobiology, Mount Sinai Hospital Research Institute, Toronto, Ontario, Canada.) Journal of immunology (Baltimore, Md. : 1950), **(1989 Jun 1)** Vol. 142, No. 11, pp. 4079-84.
Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States.
Language: English.

AB We have targeted CD4+ cytotoxic Th (Th/c) lymphocytes to a B cell lymphoma, through the use of a bispecific **antibody** containing

binding sites for both the CD3 complex on the Th/c and the Id on the surface Ig of the B lymphoma (anti-CD3-anti-Id). Cloned, keyhole limpet hemocyanin (KLH)-specific Th/c cells were nonspecifically activated by the anti-CD3-anti-Id **conjugate** to lyse the Id+ B lymphoma A20-HL. This cytotoxicity was not inhibited by **antibodies** to CD4 or LFA-1 alpha molecules. The anti-CD3-anti-Id **conjugates** also induced non-lytic Th clones to become cytotoxic, a function not elicited when these cells were activated specifically by Ag. We compare this model to our previously described system where we targeted the KLH-specific Th/c cells to the Id+ B lymphoma A20-HL via a **conjugate** consisting of KLH covalently linked to the anti-Id **antibody** (KLH-anti-Id). The mechanism involved processing and presentation of KLH by the A20-HL target. This Ag-specific cytotoxicity was **MHC class II** restricted and was inhibited by **antibodies** to the CD4 molecule. In both systems, activation of the Th/c cells resulted in bystander killing of tumor but not normal targets. These results may have important implications for the use of Th/c cells in tumor immunotherapy.

L20 ANSWER 20 OF 21 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN

1989:337207 Document No.: PREV198988040207; BA88:40207. THE **TARGETING** OF CD4-POSITIVE T LYMPHOCYTES TO A B CELL LYMPHOMA A COMPARISON OF ANTI-CD3-ANTI-IDIOTYPE **ANTIBODY CONJUGATES** AND ANTIGEN-ANTI-IDIOTYPE **ANTIBODY CONJUGATES**. GRAVELLE M [Reprint author]; OCHI A. DIV MOL IMMUNOL NEUROBIOL, MT SINAI HOSP RES INST, 600 UNIVERSITY AVE, TORONTO, ONTARIO, M4G 1X5, CANADA. Journal of Immunology, (**1989**) Vol. 142, No. 11, pp. 3079-4084. CODEN: JOIMA3. ISSN: 0022-1767. Language: ENGLISH.

AB We have targeted CD4+ cytotoxic Th (Th/c) lymphocytes to a B cell lymphoma, through the use of a bispecific **antibody** containing binding sites for both the CD3 complex on the Th/c and the Id on the surface Ig of the B lymphoma (anti-CD3-anti-Id). Cloned, keyhole limpet hemocyanin (KLH)-specific Th/c cells were nonspecifically activated by the anti-CD3-anti-Id **conjugate** to lyse the Id+ B lymphoma A20-HL. This cytotoxicity was not inhibited by **antibodies** to CD4 or LFA-1α molecules. The anti-CD3-anti-Id **conjugates** also induced non-lytic Th clones to become cytotoxic, a function not elicited when these cells were activated specifically by Ag. We compare this model to our previously described system where we targeted the KLH-specific Th/c cells to the If+ B lymphoma A20-HL via a **conjugate** consisting of KLH covalently linked to the anti-Id **antibody** KLH covalently linked to the anti-Id **antibody** (KLH-anti-Id). The mechanism involved processing and presentation of KLH by the A20-HL target. This Ag-specific cytotoxicity was **MHC class II** restricted and was inhibited by **antibodies** to the CD4 molecule. In both systems, activation of the Th/c cells resulted in bystander killing of tumor but not normal targets. These results may have important implications for the use of Th/c cells in tumor immunotherapy.

L20 ANSWER 21 OF 21 MEDLINE on STN

1989307351. PubMed ID: 3075588. Antigen-presenting function of B lymphocytes. Pierce S K; Morris J F; Grusby M J; Kaumaya P; van Buskirk A; Srinivasan M; Crump B; Smolenski L A. (Department of Biochemistry, Molecular Biology and Cell Biology, Northwestern University, Evanston, IL 60208.) Immunological reviews, **(1988 Dec)** Vol. 106, pp. 149-80. Ref: 74. Journal code: 7702118. ISSN: 0105-2896. Pub. country: Denmark. Language: English.

AB Here we review our current results studying B cells as APC and the mechanisms by which processed antigen is transported to and held on the cell surface for recognition by the specific T cell along with the **MHC class II** molecules. These studies were carried out using the globular protein cytochrome c as antigen for which

the T-cell antigenic determinant was localized to a C-terminal 10-amino acid peptide fragment. For certain analyses, native cytochrome c or antigenic peptide fragments were covalently coupled to **antibodies** directed toward B-cell surface structures, allowing the **targeting** of antigen to the APC surface. Our findings indicate that all B cells function as APC and that the APC function is not differentially regulated in defined B-cell subpopulations. Using cytochrome c-**antibody conjugates**, it was shown that the surface Ig plays two significant roles in augmenting the B-cell APC function following antigen binding: signalling for enhanced APC function and concentrating antigen for subsequent internalization and processing. Both IgM and IgD appear to function identically in facilitating antigen processing in both immune and nonimmune B-cell populations. Furthermore, the surface Ig does not appear to be specially differentiated to function in concentrating antigen, as antigen artificially bound to other B-cell surface structures including MHC class I and class II molecules is also effectively presented. Lastly, evidence is presented that a previously described B-cell activating factor activity is strongly associated with the membranes of activated but not unactivated helper T cells, providing a mechanism by which the T-cell helper function can be focused on the specific antigen-presenting B cell. Concerning the mechanism by which processed antigen is presented at the B-cell surface, evidence is presented suggesting a role of peptide-binding chaperone proteins which may function to transport peptide to the APC surface and facilitate its association with the appropriate Ia. One candidate protein, PBP72/74, is described which binds peptides but not native antigens, is a member of the hsp70 family and appears to play a role in antigen presentation by the ability of antisera raised against it to block APC functions. Peptide-**antibody conjugates** were used to explore the spacial restrictions on MHC-restricted peptide presentation and it was shown that peptides covalently coupled to **antibodies** specific for Ig, class I or class II molecules are effective antigens in vitro even in the absence of processing.(ABSTRACT TRUNCATED AT 400 WORDS)

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L21         19 L2 AND CD205

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PROCESSING COMPLETED FOR L21
L22          8 DUP REMOVE L21 (11 DUPLICATES REMOVED)

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L22  ANSWER 1 OF 8  SCISEARCH  COPYRIGHT (c) 2009 The Thomson Corporation  on
     STN
2008:1088608   The Genuine Article (R) Number: 340YE. CD11c provides an
     effective immunotarget for the generation of both CD4 and CD8 T cell
     responses.
     Glennie, Martin J. (Reprint). Univ Southampton, Sch Med, Gen Hosp, Tenovus
     Res Lab, Canc Sci Div, Southampton SO16 6YD, Hants, England (Reprint).
     Castro, Fernanda V. V.; Tutt, Alison L.; White, Ann L.; Teeling, Jessica
     L.; James, Sonya; French, Ruth R.. Univ Southampton, Sch Med, Canc Sci
     Div, Tenovus Res Lab, Southampton SO16 6YD, Hants, England; Univ
     Southampton, Sch Med, Sch Biol Sci, CNS Grp, Southampton SO16 6YD, Hants,
     England. E-mail: mjg@soton.ac.uk.
     EUROPEAN JOURNAL OF IMMUNOLOGY (AUG 2008) Vol. 38, No. 8, pp. 2263-2273.
     ISSN: 0014-2980. Publisher: WILEY-V C H VERLAG GMBH, PO BOX 10 11 61,
     D-69451 WEINHEIM, GERMANY. Language: English.
     *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*
AB        The magnitude and quality of T cell responses generated when Ag is
     targeted to receptors on DC is influenced by both the specific receptor
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targeted and its distribution among DC subsets. Here we examine the targeting of the model Ag OVA to potential DC targets, including CD11c, **CD205**, MHC class II, CD40, TLR2 and Fc gamma RII/III, using a panel of (Fab' x OVA) **conjugates**. In vitro studies identified CD11c, **CD205** and MHC class 11 as superior and comparably effective immunotargets for the delivery of OVA to APC for presentation to T cells. In vivo studies, however, showed a marked advantage of targeting Ag to CD11c for both CD4 (OT-II) and CD8 (OT-1) responses, with robust stimulation after a single, low dose (equivalent to 0.5 pg OVA); in contrast, (anti-**CD205** x OVA) and (anti-MHC class II x OVA) resulted in markedly less proliferation of both OT-I and OT-II cells. Biodistribution and immunohistochernical studies suggest that the exceptional ability of CD11c to capture Ag in lymphoid tissues may, at least partially, explain its ability to promote T cell responses. These results suggest that targeting antigen via CD11c offers a previously unappreciated strategy for vaccine development which, unlike most targets, delivers robust responses of both CD4 and CD8 T cells.

L22 ANSWER 2 OF 8 MEDLINE on STN DUPLICATE 1

2007765355. PubMed ID: 18081041. Broad T cell immunity to the LcrV virulence protein is induced by targeted delivery to DEC-205/**CD205** -positive mouse dendritic cells. Do Yoonkyung; Park Chae Gyu; Kang Young-Sun; Park Sung Ho; Lynch Rebecca M; Lee Haekyung; Powell Bradford S; Steinman Ralph M. (Laboratory of Cellular Physiology and Immunology and Chris Browne Center for Immunology and Immune Diseases, The Rockefeller University, New York 10065-6399, USA.) European journal of immunology, (2008 Jan) Vol. 38, No. 1, pp. 20-9. Journal code: 1273201. ISSN: 0014-2980. Pub. country: Germany: Germany, Federal Republic of. Language: English.

AB There is a need for a more efficient vaccine against the bacterium Yersinia pestis, the agent of pneumonic plague. The F1-LcrV (F1-V) subunit vaccine in alhydrogel is known to induce humoral immunity. In this study, we utilized DC to investigate cellular immunity. We genetically engineered the LcrV virulence protein into the anti-DEC-205/ **CD205** mAb and thereby targeted the **conjugated** protein directly to mouse DEC-205(+) DC in situ. We observed antigen-specific CD4(+) T cell immunity measured by intracellular staining for IFN-gamma in three different mouse strains (C57BL/6, BALB/c, and C3H/HeJ), while we could not observe such T cell responses with F1-V vaccine in alhydrogel. Using a peptide library for LcrV protein, we identified two or more distinct CD4(+) T cell mimetopes in each MHC haplotype, consistent with the induction of broad immunity. When compared to nontargeted standard protein vaccine, DC targeting greatly increased the efficiency for inducing IFN-gamma-producing T cells. The targeted LcrV protein induced **antibody** responses to a similar extent as the F1-V subunit vaccine, but Th1-dependent IgG2a and IgG2c isotypes were observed only after anti-DEC-205:LcrV mAb immunization. This study sets the stage for the analysis of functional roles of IFN-gamma-producing T cells in Y. pestis infection.

L22 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2009 ACS on STN

2007:906284 Document No. 147:275679 Polypeptide **conjugates** of HLA-G histocompatibility antigens with ligand binding moieties and their transgenic expression in embryonic stem cells. Walsh, James (Axordia Limited, UK). PCT Int. Appl. WO 2007091078 A2 20070816, 93pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC,

ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2007-GB448 20070208. PRIORITY: GB 2006-2688 20060210; GB 2006-5180 20060315.

AB Polypeptide **conjugates** comprising human histocompatibility antigen HLA-G fused to ligand binding moieties, such as single-chain variable fragment **antibody** derivs., enable the targeting of HLA-G to specific cell types and the use of the **conjugates** in the treatment of conditions that would benefit from the inhibition of T cell-mediated responses. The ectopic expression of HLA-G encoding nucleic acid mols. in human embryoic stem cells is also disclosed, and these transfected cells can be used to induce immune tolerance of the stem cells. A problem associated with gene therapy and/or tissue engineering is the provision of cell/tissue materials that do not induce a natural killer cell response in the recipient animal. The provision of stem cell lines that either constitutively express or developmentally express HLA-G genes will facilitate procedures that involve gene and tissue replacement therapy.

L22 ANSWER 4 OF 8 MEDLINE on STN DUPLICATE 2

2007621035. PubMed ID: 17947679. The novel endocytic and phagocytic C-Type lectin receptor DCL-1/CD302 on macrophages is colocalized with F-actin, suggesting a role in cell adhesion and migration. Kato Masato; Khan Seema; d'Aniello Elisabetta; McDonald Kylie J; Hart Derek N J. (Dendritic Cell Program, Mater Medical Research Institute, South Brisbane, Queensland, Australia.) Journal of immunology (Baltimore, Md. : 1950), (2007 Nov 1) Vol. 179, No. 9, pp. 6052-63. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB C-type lectin receptors play important roles in mononuclear phagocytes, which link innate and adaptive immunity. In this study we describe characterization of the novel type I transmembrane C-type lectin DCL-1/CD302 at the molecular and cellular levels. DCL-1 protein was highly conserved among the human, mouse, and rat orthologs. The human DCL-1 (hDCl-1) gene, composed of six exons, was located in a cluster of type I transmembrane C-type lectin genes on chromosomal band 2q24. Multiple tissue expression array, RT-PCR, and FACS analysis using new anti-hDCL-1 mAbs established that DCL-1 expression in leukocytes was restricted to monocytes, macrophages, granulocytes, and dendritic cells, although DCL-1 mRNA was present in many tissues. Stable hDCL-1 Chinese hamster ovary cell transfectants endocytosed FITC-**conjugated** anti-hDCL-1 mAb rapidly (t(1/2) = 20 min) and phagocytosed anti-hDCL-1 mAb-coated microbeads, indicating that DCL-1 may act as an Ag uptake receptor. However, anti-DCL-1 mAb-coated microbead binding and subsequent phagocytic uptake by macrophages was approximately 8-fold less efficient than that of anti-macrophage mannose receptor (MMR/CD206) or anti-DEC-205/**CD205** mAb-coated microbeads. Confocal studies showed that DCL-1 colocalized with F-actin in filopodia, lamellipodia, and podosomes in macrophages and that this was unaffected by cytochalasin D, whereas the MMR/CD206 and DEC-205/**CD205** did not colocalize with F-actin. Furthermore, when transiently expressed in COS-1 cells, DCL-1-EGFP colocalized with F-actin at the cellular cortex and microvilli. These data suggest that hDCL-1 is an unconventional lectin receptor that plays roles not only in endocytosis/phagocytosis but also in cell adhesion and migration and thus may become a target for therapeutic manipulation.

L22 ANSWER 5 OF 8 EMBASE DUPLICATE 3

2006382991 EMBASE Preferential induction of CD4(+) T cell responses through in vivo targeting of antigen to dendritic cell-associated C-type lectin-1. Carter, Robert W.; Thompson, Clare; Reid, Delyth M.; Wong, Simon Y. C.; Tough, David F., Dr. (correspondence). Edward Jenner Institute for Vaccine Research, Compton, Newbury, Berkshire RG20 7NN, United Kingdom. david.toug h@jenner.ac.uk. Reid, Delyth M.. Department of Ophthalmology, Institute of

Medical Sciences, Aberdeen University, Foresterhill, Aberdeen AB25 2ZD, United Kingdom. Wong, Simon Y. C.. Department of Medicine and Therapeutics, Institute of Medical Sciences, Aberdeen University, Foresterhill, Aberdeen AB25 2ZD, United Kingdom.
Journal of Immunology Vol. 177, No. 4, pp. 2276-2284 15 Aug 2006.
Refs: 51.
ISSN: 0022-1767. CODEN: JOIMA3.
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20060828. Last Updated on STN: 20060828

AB Targeting of Ags and therapeutics to dendritic cells (DCs) has immense potential for immunotherapy and vaccination. Because DCs are heterogeneous, optimal targeting strategies will require knowledge about functional specialization among DC subpopulations and identification of molecules for targeting appropriate DCs. We characterized the expression of a fungal recognition receptor, DC-associated C-type lectin-1 (Dectin-1), on mouse DC subpopulations and investigated the ability of an anti-Dectin-1 Ab to deliver Ag for the stimulation of immune responses. Dectin-1 was shown to be expressed on CD8α(-)CD4(-)CD11b(+) DCs found in spleen and lymph nodes and dermal DCs present in skin and s.c. lymph nodes. Injection of Ag-anti-Dectin-1 **conjugates** induced CD4(+) and CD8(+) T cell and Ab responses at low doses where free Ag failed to elicit a response. Notably, qualitatively different immune responses were generated by targeting Ag to Dectin-1 vs **CD205**, a molecule expressed on CD8α(+)CD4- CD11b(+) DCs, dermal DCs, and Langerhans cells. Unlike anti-Dectin-1, anti-**CD205** **conjugates** failed to elicit an Ab response. Moreover, when **conjugates** were injected i.V., anti-Dectin-1 stimulated a much stronger CD4(+) T cell response and a much weaker CD8(+) T cell response than anti-**CD205**. The results reveal Dectin-1 as a potential targeting molecule for immunization and have implications for the specialization of DC subpopulations.

L22 ANSWER 6 OF 8 MEDLINE on STN DUPLICATE 4
2005692821. PubMed ID: 16361439. Network of dendritic cells within the muscular layer of the mouse intestine. Flores-Langarica Adriana; Meza-Perez Selene; Calderon-Amador Juana; Estrada-Garcia Teresa; Macpherson Gordon; Lebecque Serge; Saeland Sem; Steinman Ralph M; Flores-Romo Leopoldo. (Department of Immunology, Escuela Nacional de Ciencias Biologicas del Instituto Politecnico Nacional, Prolongacion de Carpio y Plan de Ayala, Casco de Santo Tomas, 11340, Mexico.) Proceedings of the National Academy of Sciences of the United States of America, (2005 Dec 27) Vol. 102, No. 52, pp. 19039-44. Electronic Publication: 2005-12-16. Journal code: 7505876. ISSN: 0027-8424.
Report No.: NLM-PMC1316057. Pub. country: United States. Language: English.

AB Dendritic cells (DCs) are located at body surfaces such as the skin, respiratory and genital tracts, and intestine. To further analyze intestinal DCs, we adapted an epidermal sheet separation technique and obtained two intestinal layers, facing the lumen and serosa. Unexpectedly, immunolabeling of the layer toward the serosa revealed a regular, dense, planar network of cells with prominent dendritic morphology within the external muscular layer and with increasing frequency along the length of the intestine. Direct examination of the serosal-disposed layers showed a significant fraction of the DCs to express DEC-205/**CD205**, CD11c, Langerin/CD207, Fcgamma receptor/CD16/32, CD14, and low levels of activation markers, CD25, CD80, CD86, and CD95. By more sensitive FACS analyses, cells from this layer contained two CD11c(+) populations of CD45(+) **CD205**(+), CD19(-) leukocytes, MHC II(+) and MHC II(-). When ovalbumin **conjugated** to an anti-DEC-205 **antibody** was injected into mice, the **conjugate** targeted to these DCs, which upon isolation were able to

stimulate ovalbumin-specific, CD4(+) and CD8(+) T cell antigen receptor-transgenic T cells. In vivo, these DCs responded to two microbial stimuli, systemic LPS and oral live bacteria, by up-regulating CD80, CD86, DEC-205, and Langerin within 12 h. This network of DCs thus represents a previously unrecognized antigen-presenting cell system in the intestine.

L22 ANSWER 7 OF 8 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN
2006:182484 Document No.: PREV200600184596. A novel C-type lectin receptor DCL-1 (CD302) is a potential endocytic receptor for tumor antigen loading into antigen presenting cells. Kato, Masato [Reprint Author]; Khan, Seema; McDonald, Kylie J.; Hart, Derek N. J.. Mater Med Res Inst, Brisbane, Qld, Australia. Blood, (NOV 16 2005) Vol. 106, No. 11, Part 1, pp. 628A. Meeting Info.: 47th Annual Meeting of the American-Society-of-Hematology. Atlanta, GA, USA. December 10 -13, 2005. Amer Soc Hematol. CODEN: BLOOAW. ISSN: 0006-4971. Language: English.

AB DCL-1 (CD302) is a novel C-type lectin receptor, discovered as a genetic fusion partner of DEC-205 (**CD205**), a C-type lectin that delivers antigen from the surface into DC antigen processing pathway (J. Biol. Chemical 2003. 278:34035). We have now examined the molecular nature and expression of DCL-1. DCL-1 contains an external single C-type lectin-like domain followed by a transmembrane and cytoplasmic domain with putative signaling and endocytic motifs. The DCL-1 gene, consisting of 6 exons, was mapped to chromosome 2q24, approximately 5 kb downstream of the DEC-205 gene. Human DCL-1 has 76% protein identity to the mouse ortholog, suggesting its highly conserved function. Northern blot analysis showed that the 4.2 kb DCL-1 mRNA was present in myeloid cell lines, but not in T and B cell lines. Specialized phagocytic cells (i.e. monocytes, macrophages, granulocytes), monocyte-derived DC (MoDC) and blood DC (BDC) expressed DCL-1 mRNA, detected by RT-PCR. Immunoprecipitation/Western blot (IP/WB) analysis using FLAG-tagged DCL-1 transfectants detected a broad band (modal size 35 kDa), which became a single 26 kDa band after N-glycosidase F digestion, indicating that DCL-1 is N-glycosylated. Flow cytometry studies with DCL-1 mAb (MMRI-20, developed in house) detected moderate levels of DCL-1 expression on granulocytes, monocytes, macrophages, MoDC and BDC, but not on lymphoid cells. Concomitant WB/IP analysis using the DCL-1 mAb detected 26 and 33 kDa doublets in monocytes, macrophages and MoDC. DCL-1 transfectants, macrophages, MoDC and BDC endocytosed cell surface DCL-1 after crosslinking with the DCL-1 mAb. DCL-1-Ig fusion protein bound to GlcNAc- and Man-**conjugated** beads, but not to GalNAc-, Fuc- and mannan-**conjugated** beads in a calcium-dependent manner. Thus, DCL-1 is expressed by phagocytes and DC, behaves as a C-type lectin, and is likely to be involved in endocytosis/phagocytosis of microbes. We are exploiting DCL-1 as a potential antigen-loading receptor for DC tumor immunotherapy. This work is supported by National Health and Medical Research Council of Australia.

L22 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2009 ACS on STN
2003:118018 Document No. 138:168835 Targeting of an antigen presenting cell (APC) with a modulator of T cell signalling, such as a Notch ligand, coupled to the MHC class II-binding motif from a superantigen. Bodmer, Mark William; Champion, Brian Robert; McKenzie, Grahame James; Nye, Lucy Emma (Lorantis Limited, UK). PCT Int. Appl. WO 2003012111 A2 20030213, 93 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-GB3381 20020725. PRIORITY: GB 2001-18155 20010725.

AB The present invention relates to the concept of delivering a modulator of T cell signaling, such as a Notch ligand, to an antigen presenting cell (APC). The targeting approach disclosed uses, for example, the major histocompatibility complex (MHC) class II binding motif from a superantigen coupled to a modulator of the Notch signaling pathway. Superantigens bind both MHC class II mols. and subsets of T cell receptors and thus effectively cross-link APCs to T cells and activate cells polyclonally. The mol. regions of these mols. that impart T cell receptor (TCR) and MHC class II binding have been defined structurally and have been shown to be distinct regions of the mol. By using the MHC class II binding domain with a modulator of the Notch signaling pathway we can focus the activity of the Notch signaling pathway modulator to the APCs at the site of delivery. Further, the domain lacks toxin activity because it cannot find the T cell receptor to activate T cells. According to one aspect of the present invention there is provided a **conjugate** comprising a first and a second sequence wherein the first sequence comprises a polypeptide which is capable of binding to an APC, or a polynucleotide encoding therefor, and the second sequence comprises a polypeptide comprising a modulator of a signaling pathway in a T cell or a polynucleotide encoding therefor.

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L24 5 DUP REMOVE L23 (0 DUPLICATES REMOVED)

=> d l24 1-5 cbib abs

L24 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2009 ACS on STN
2009:583278 Document No. 150:537922 Human anti-DEC-205 receptor **antibodies** and antigen **conjugates** for diagnosis and treatment of inflammation, infection, allergy, cancer and autoimmune disease. Keler, Tibor; He, Lizhen; Ramakrishna, Venky; Vitale, Laura A. (Celldex Therapeutics Inc., USA). PCT Int. Appl. WO 2009061996 A2 20090514, 109pp. DESIGNATED STATES: W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, MT, NE, NL, NO, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2008-US82745 20081107. PRIORITY: US 2007-2253P 20071107; US 2008-191551P 20080910.
AB Isolated monoclonal **antibodies** which bind to human DEC-205 (dendritic and epithelial cell 205) receptor and related **antibody** -based compns. and mols. are disclosed. Also disclosed are pharmaceutical compns. comprising the **antibodies**, as well as therapeutic and diagnostic methods for using the **antibodies**.

L24 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2009 ACS on STN
2005:690696 Document No. 143:210178 Targeting of Antigens to Activated Dendritic Cells In vivo Cures Metastatic Melanoma in Mice. Mahnke, Karsten; Qian, Yingjie; Fondel, Sabine; Brueck, Juergen; Becker, Christian; Enk, Alexander H. (Department of Dermatology, University of Heidelberg, Heidelberg, Germany). Cancer Research, 65(15), 7007-7012 (English) 2005. CODEN: CNREA8. ISSN: 0008-5472. Publisher: American Association for Cancer Research.
AB Anti (α)-DEC-205 **antibodies** target to the DEC-205 receptor

that mediates antigen presentation to T cells by dendritic cells. To exploit these properties for immunization purposes, we **conjugated** the melanoma antigen tyrosinase-related protein (TRP)-2 to αDEC-205 **antibodies** and immunized mice with these **conjugates** together with dendritic cell-activating oligonucleotides (CpG). Upon injection of the melanoma cell line B16, αDEC-TRP immunized mice were protected against tumor growth. Even more important for clin. applications, we were able to substantially slow the growth of implanted B16 cells by injection of αDEC-TRP2 **conjugates** into tumor bearing hosts. Approx. 70% of the animals were cured from existing tumors by treatment with αDEC **conjugates** carrying two different melanoma antigens (TRP-2 and gp100). This protection was due to induction of melanoma-specific CD4 and CD8 responses. Thus, these data show that targeting of dendritic cells in situ by the means of **antibody** -antigen **conjugates** may be a novel way to induce long-lasting antitumor immunity.

L24 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2009 ACS on STN
2004:1126838 Document No. 142:73405 Vaccines comprising anti-DEC-205 **antibody**-antigen **conjugates** with or without dendritic cell maturation factor for enhancing long lasting antigen presentation or inducing tolerance. Hawiger, Daniel; Nussenzweig, Michel; Steinman, Ralph M.; Bonifaz, Laura (USA). U.S. Pat. Appl. Publ. US 20040258688 A1 20041223, 116 pp., Cont.-in-part of U.S. Ser. No. 925,284. (English). CODEN: USXXCO. APPLICATION: US 2004-800023 20040312. PRIORITY: US 1995-381528 19950131; WO 1996-US1383 19960131; US 2000-586704 20000605; US 2001-925284 20010809.

AB The present invention relates to methods for targeting antigen to antigen presenting cells through specific endocytic receptors, which results in persistent antigen presentation in the context of MHC mols. Such highly efficient antigen presentation results in robust and long lasting immune responses, in particular cell mediated responses. The invention provides for immune compns. containing **antibodies** to DEC-205 in combination with the antigen for eliciting either T cell mediated immunity when delivered with a dendritic cell maturation factor, or for inducing tolerance when delivered in the absence of a dendritic cell maturation factor. The antigen is tumor antigen or pathogenic antigen; and the dendritic cell maturation factor is anti-CD4 **antibody**, inflammatory cytokine, polyI/C, single stranded RNA, DNA, CpG, ligation of IL-1, TNF or TOLL-like receptor, TRAF-6 or NF-κB. The compns. described in the present invention are effective as a single dose at low concns. and show efficacy even with non-replicating subunit vaccines.

L24 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2009 ACS on STN
2004:242388 Document No. 140:337856 In vivo targeting of antigens to maturing dendritic cells via the DEC-205 receptor improves T cell vaccination. Bonifaz, Laura C.; Bonnyay, David P.; Charalambous, Anna; Darguste, Dara I.; Fujii, Shin-Ichiro; Soares, Helena; Brimnes, Marie K.; Moltedo, Bruno; Moran, Thomas M.; Steinman, Ralph M. (Laboratory of Cellular Physiology and Immunology, Chris Browne Center for Immunology and Immune Diseases, The Rockefeller University, New York, NY, 10021, USA). Journal of Experimental Medicine, 199(6), 815-824 (English) 2004. CODEN: JEMEAV. ISSN: 0022-1007. Publisher: Rockefeller University Press.

AB The prevention and treatment of prevalent infectious diseases and tumors should benefit from improvements in the induction of antigen-specific T cell immunity. To assess the potential of antigen targeting to dendritic cells to improve immunity, we incorporated ovalbumin protein into a monoclonal **antibody** to the DEC-205 receptor, an endocytic receptor that is abundant on these cells in lymphoid tissues. Simultaneously, we injected agonistic α-CD40 **antibody** to mature the dendritic cells. We found that a single low dose of **antibody-conjugated** ovalbumin initiated immunity from

the naive CD4+ and CD8+ T cell repertoire. Unexpectedly, the αDEC-205 antigen **conjugates**, given s.c., targeted to dendritic cells systemically and for long periods, and ovalbumin peptide was presented on MHC class I for 2 wk. This was associated with stronger CD8+ T cell-mediated immunity relative to other forms of antigen delivery, even when the latter was given at a thousand times higher doses. In parallel, the mice showed enhanced resistance to an established rapidly growing tumor and to viral infection at a mucosal site. By better harnessing the immunizing functions of maturing dendritic cells, **antibody**-mediated antigen targeting via the DEC-205 receptor increases the efficiency of vaccination for T cell immunity, including systemic and mucosal resistance in disease models.

L24 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2009 ACS on STN
2002:946830 Document No. 138:23657 Enhanced antigen delivery and modulation of the immune response using antigen/anti-DEC-205 **antibody conjugates**. Hawiger, Daniel; Nussenzweig, Michel C.; Steinman, Ralph M. (USA). U.S. Pat. Appl. Publ. US 20020187131 A1 20021212, 19 pp., Cont.-in-part of U.S. Ser. No. 586,704. (English). CODEN: USXXCO. APPLICATION: US 2001-925284 20010809. PRIORITY: US 1995-381528 19950131; US 2000-586704 20000605.

AB Methods are provided for the enhanced delivery of an antigen to antigen-presenting cells such as dendritic cells by conjugating an antigen to a mol. targeted to an endocytic receptor on the dendritic cell, such as DEC-205. The mol. targeted to an endocytic receptor may be a natural ligand to the receptor or an **antibody** thereto. **Conjugates** may be covalent complexes or single-chain polypeptides. The antigen/anti-DEC-205 **antibody conjugate** plus an agonistic anti-CD40 **antibody** induces persistent T-cell activation, whereas the **conjugate** without the anti-CD40 **antibody** induces tolerance. The agonistic anti-CD40 **antibody** promotes maturation of the dendritic cells.

=> s l2 and CD204
L25 1 L2 AND CD204

=> d l25 cbib abs

L25 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2009 ACS on STN
2003:118018 Document No. 138:168835 Targeting of an antigen presenting cell (APC) with a modulator of T cell signalling, such as a Notch ligand, coupled to the MHC class II-binding motif from a superantigen. Bodmer, Mark William; Champion, Brian Robert; McKenzie, Grahame James; Nye, Lucy Emma (Lorantis Limited, UK). PCT Int. Appl. WO 2003012111 A2 20030213, 93 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-GB3381 20020725. PRIORITY: GB 2001-18155 20010725.

AB The present invention relates to the concept of delivering a modulator of T cell signaling, such as a Notch ligand, to an antigen presenting cell (APC). The targeting approach disclosed uses, for example, the major histocompatibility complex (MHC) class II binding motif from a superantigen coupled to a modulator of the Notch signaling pathway. Superantigens bind both MHC class II mols. and subsets of T cell receptors and thus effectively cross-link APCs to T cells and activate cells polyclonally. The mol. regions of these mols. that impart T cell receptor

(TCR) and MHC class II binding have been defined structurally and have been shown to be distinct regions of the mol. By using the MHC class II binding domain with a modulator of the Notch signaling pathway we can focus the activity of the Notch signaling pathway modulator to the APCs at the site of delivery. Further, the domain lacks toxin activity because it cannot find the T cell receptor to activate T cells. According to one aspect of the present invention there is provided a **conjugate** comprising a first and a second sequence wherein the first sequence comprises a polypeptide which is capable of binding to an APC, or a polynucleotide encoding therefor, and the second sequence comprises a polypeptide comprising a modulator of a signaling pathway in a T cell or a polynucleotide encoding therefor.

=> s l2 and CD14
L26 501 L2 AND CD14

=> s l26 and notch ligand
L27 2 L26 AND NOTCH LIGAND

=> dup remove l27
PROCESSING COMPLETED FOR L27
L28 2 DUP REMOVE L27 (0 DUPLICATES REMOVED)

=> d l28 1-2 cbib abs

L28 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2009 ACS on STN
2008:889295 Document No. 149:191990 Solid tumor stem cell xenograft model and uses thereof. Clarke, Michael F.; Dylla, Scott J.; Satyal, Sanjeev (The Regents of the University of Michigan, USA). U.S. Pat. Appl. Publ. US 20080178305 A1 20080724, 80pp., Cont.-in-part of U.S. Ser. No. 529,869. (English). CODEN: USXXCO. APPLICATION: US 2007-776935 20070712. PRIORITY: US 2000-222794P 20000803; US 2000-240317P 20001013; US 2001-920517 20010801; WO 2001-US24243 20010802; US 2003-343692 20030825; US 2006-529869 20060929.

AB A small percentage of cells within an established solid tumor have the properties of stem cells. These solid tumor stem cells give rise both to more tumor stem cells and to the majority of cells in the tumor that have lost the capacity for extensive proliferation and the ability to give rise to new tumors. Thus, solid tumor heterogeneity reflects the presence of tumor cell progeny arising from a solid tumor stem cell. We have developed a xenograft model in which we have been able to establish tumors from primary tumors via injection of tumor cells in the mammary gland of severely immunodeficient mice. These xenograft assays have allowed us to do biol. and mol. assays to characterize clonogenic solid tumor stem cells. We have also developed evidence that strongly implicates the Notch pathway, especially Notch 4, as playing a central pathway in carcinogenesis. The invention also provides a way that anticancer therapies can be directed against the solid tumor stem cells. The invention provides e.g. a method for diagnosing the effect of a therapeutic compound on solid tumor stem cells from a solid tumor of epithelial origin.

L28 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2009 ACS on STN
2003:118018 Document No. 138:168835 Targeting of an antigen presenting cell (APC) with a modulator of T cell signalling, such as a **Notch ligand**, coupled to the MHC class II-binding motif from a superantigen. Bodmer, Mark William; Champion, Brian Robert; McKenzie, Grahame James; Nye, Lucy Emma (Lorantis Limited, UK). PCT Int. Appl. WO 2003012111 A2 20030213, 93 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX,

MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-GB3381 20020725. PRIORITY: GB 2001-18155 20010725.

AB The present invention relates to the concept of delivering a modulator of T cell signaling, such as a **Notch ligand**, to an antigen presenting cell (APC). The targeting approach disclosed uses, for example, the major histocompatibility complex (MHC) class II binding motif from a superantigen coupled to a modulator of the Notch signaling pathway. Superantigens bind both MHC class II mols. and subsets of T cell receptors and thus effectively cross-link APCs to T cells and activate cells polyclonally. The mol. regions of these mols. that impart T cell receptor (TCR) and MHC class II binding have been defined structurally and have been shown to be distinct regions of the mol. By using the MHC class II binding domain with a modulator of the Notch signaling pathway we can focus the activity of the Notch signaling pathway modulator to the APCs at the site of delivery. Further, the domain lacks toxin activity because it cannot find the T cell receptor to activate T cells. According to one aspect of the present invention there is provided a **conjugate** comprising a first and a second sequence wherein the first sequence comprises a polypeptide which is capable of binding to an APC, or a polynucleotide encoding therefor, and the second sequence comprises a polypeptide comprising a modulator of a signaling pathway in a T cell or a polynucleotide encoding therefor.

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=> s l2 and TLR
L29        146 L2 AND TLR

=> s l29 and notch delta
L30          0 L29 AND NOTCH DELTA

=> s l29 and jagged 1
L31          1 L29 AND JAGGED 1

=> d l31 cbib abs
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L31 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2009 ACS on STN

2005:673420 Document No. 143:167623 Expression profiles of endothelial cells in response to TNF-α, IL-1β, and IL-8, methods of assessing a tissue inflammatory response using the same, and diagnostic and therapeutic uses. Smith, Steven Kevin; Charnock-Jones, David Stephen; Print, Cristin Gregor; Johnson, Nicola Anne (Cambridge University Technical Services Limited, UK). PCT Int. Appl. WO 2005068655 A2 20050728, 492 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-GB57 20050114. PRIORITY: GB 2004-976 20040116.

AB The invention provides methods of assessing a tissue inflammatory response, comprising making a quant. determination of the level of at least five transcripts shown in transcriptome provided in the invention or proteins encoded thereby, in a sample; and comparing the abundance of said transcripts or proteins so determined with the level of said transcript obtained from a control sample. Methods for diagnosis of a condition with

which a tissue inflammatory response is associated are also provided, as are gene chip arrays and protein based assays suitable for use in these methods. Assay methods for determining a modulator of a tissue inflammatory response or a condition associated therewith also form part of the invention. The gene expression was profiled in human umbilical vein endothelial cells (HUVEC) contacted with a mixture of TNF-α, interleukin-1β, and interleukin-8. In addition, expression in different endothelial cells types obtained from different parts of the body, namely HUVEC, human coronary artery endothelial cells (HCAEC) and human uterine microvascular endothelial cells (UtMVEC) were analyzed. It was found that many transcripts were consistently regulated by inflammatory signals in all three cell types.

=> s l2 and langerin
L32 18 L2 AND LANGERIN

=> dup remove l32
PROCESSING COMPLETED FOR L32
L33 7 DUP REMOVE L32 (11 DUPLICATES REMOVED)

=> d l33 1-7 cbib abs

L33 ANSWER 1 OF 7 MEDLINE on STN DUPLICATE 1
2009468143. PubMed ID: 19580475. Migration of skin dendritic cells in response to ionizing radiation exposure. Cummings Ryan J; Mitra Soumya; Foster Thomas H; Lord Edith M. (Department of Microbiology, University of Rochester Medical Center, Rochester, New York 14642, USA.) Radiation research, (2009 Jun) Vol. 171, No. 6, pp. 687-97. Journal code: 0401245. ISSN: 0033-7587. Pub. country: United States. Language: English.
AB We describe an imaging assay that monitors the migration of two unique subsets of immune dendritic cells (DC), interstitial dendritic cells (iDC) and Langerhans cells (LC), found in the dermal and epidermal layers of skin, respectively. Using this assay, we study responses of these cells to ionizing radiation. Results obtained using whole-mount histology and fluorescence microscopy suggest that ionizing radiation triggered the migration of both major histocompatibility complex (MHC) class II(+) iDC and **Langerin**(+) LC in a dose- and time-dependent manner. Migration appeared to be limited by local administration of recombinant IL-12, a potent immunostimulatory cytokine known to induce DNA repair. Those findings were extended to an in vivo model by injecting fluorescently **conjugated** anti-MHC class II **antibodies** intradermally into the ears of live, anesthetized mice and visualizing the DC population in the same ear before and after radiation exposure using confocal microscopy.

L33 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2009 ACS on STN
2005:1331738 Document No. 144:68594 Treating autoimmune diseases and viral infection by inducing antigen presentation by tolerance inducing antigen presenting cells (APCs) using autoantigen peptides linked to APC **antibodies**. Bowdish, Katherine S.; Kretz-Rommel, Anke; Dakappagari, Naveen (Alexion Pharmaceuticals, Inc., USA). U.S. Pat. Appl. Publ. US 20050281828 A1 20051222, 119 pp., Cont.-in-part of U.S. Ser. No.16,647. (English). CODEN: USXXCO. APPLICATION: US 2005-97812 20050401. PRIORITY: US 2004-16647 20041217; WO 2004-US6570 20040304; US 2004-548385P 20040228; US 2003-529500P 20031215; US 2003-451816P 20030304.
AB **Antibodies** to antigen presenting cells may be utilized to interfere with the interaction of the antigen presenting cell and immune cells, including T cells. The **antibodies** are specific to antigen-internalizing receptor such as DEC-205, mannose receptor, DC-SIGN, DC-SIGNR (DC-SIGN-related), MHC, Toll receptor, **langerin**, asialoglycoprotein receptor, β-glucan receptor, C-type lectin

receptor and dendritic cell immunoreceptor. Peptides may be linked to said **antibodies** thereby generating an immune response to such peptides. Preferably peptides linked to the **antibodies** are associated with autoimmunity. The peptide is autoantigen such as glutamic acid decarboxylase or epitope, insulin or epitope, heat shock protein or epitope, or β cell antigen or epitope. The antigen-presenting cells are dendritic cells, macrophages, endothelial cells, Kupffer cells and B-cells. The **antibodies** may also linked to toxin, or tumor toxin. Further more, vaccine comprising **antibody** to DC-SIGN or L-SIGN may prevents entry of viruses into cells. In some embodiments, the invention provides chimeric **antibodies** that recognize an L-SIGN and block binding of HIVgp120 or Ebola envelope protein to L-SIGN or DC-SIGN; **antibodies** that recognize both an L-SIGN and a DC-SIGN and block binding of HIVgp120 or Ebola envelope protein to DC-SIGN. The **antibody** may bind to the same epitope as the epitope to which the Ebola envelope protein or the HIVgp120 binds.

L33 ANSWER 3 OF 7 MEDLINE on STN DUPLICATE 2
2005692821. PubMed ID: 16361439. Network of dendritic cells within the muscular layer of the mouse intestine. Flores-Langarica Adriana; Meza-Perez Selene; Calderon-Amador Juana; Estrada-Garcia Teresa; Macpherson Gordon; Lebecque Serge; Saeland Sem; Steinman Ralph M; Flores-Romo Leopoldo. (Department of Immunology, Escuela Nacional de Ciencias Biologicas del Instituto Politecnico Nacional, Prolongacion de Carpio y Plan de Ayala, Casco de Santo Tomas, 11340, Mexico.) Proceedings of the National Academy of Sciences of the United States of America, (2005 Dec 27) Vol. 102, No. 52, pp. 19039-44. Electronic Publication: 2005-12-16. Journal code: 7505876. ISSN: 0027-8424. Report No.: NLM-PMC1316057. Pub. country: United States. Language: English.

AB Dendritic cells (DCs) are located at body surfaces such as the skin, respiratory and genital tracts, and intestine. To further analyze intestinal DCs, we adapted an epidermal sheet separation technique and obtained two intestinal layers, facing the lumen and serosa. Unexpectedly, immunolabeling of the layer toward the serosa revealed a regular, dense, planar network of cells with prominent dendritic morphology within the external muscular layer and with increasing frequency along the length of the intestine. Direct examination of the serosal-disposed layers showed a significant fraction of the DCs to express DEC-205/CD205, CD11c, **Langerin**/CD207, Fcgamma receptor/CD16/32, CD14, and low levels of activation markers, CD25, CD80, CD86, and CD95. By more sensitive FACS analyses, cells from this layer contained two CD11c(+) populations of CD45(+) CD205(+), CD19(-) leukocytes, MHC II(+) and MHC II(-). When ovalbumin **conjugated** to an anti-DEC-205 **antibody** was injected into mice, the **conjugate** targeted to these DCs, which upon isolation were able to stimulate ovalbumin-specific, CD4(+) and CD8(+) T cell antigen receptor-transgenic T cells. In vivo, these DCs responded to two microbial stimuli, systemic LPS and oral live bacteria, by up-regulating CD80, CD86, DEC-205, and **Langerin** within 12 h. This network of DCs thus represents a previously unrecognized antigen-presenting cell system in the intestine.

L33 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2009 ACS on STN
2004:902130 Document No. 141:394080 Autoantigen epitopes linked to **antibodies** for inducing antigen presentation by tolerance-inducing antigen presenting cells and for treating autoimmune diseases. Bowdish, Katherine S.; Kretz-Rommel, Anke; Dakappagari, Naveen (Alexion Pharmaceuticals, Inc., USA). PCT Int. Appl. WO 2004091543 A2 20041028, 71 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ,

LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-US6570 20040304. PRIORITY: US 2003-451816P 20030304; US 2003-529500P 20031215; US 2004-548385P 20040228.

AB **Antibodies** to antigen presenting cells may be utilized to interfere with the interaction of the antigen presenting cell and immune cells, including T cells. The **antibodies** are specific to antigen-internalizing receptor such as DEC-205, mannose receptor, DC-SIGN, DC-SIGNR, MHC, toll receptor, **langerin**, asialoglycoprotein receptor, β-glucan receptor, C-type lectin receptor and dendritic cell immunoreceptor. Peptides may be linked to said **antibodies** thereby generating an immune response to such peptides. The peptide is autoantigen such as glutamic acid decarboxylase or epitope, insulin or epitope, heat shock protein or epitope, or β cell antigen or epitope. The antigen-presenting cells are dendritic cells, macrophages, endothelial cells, Kupffer cells and B cells. The **antibodies** may also linked to toxin, or tumor toxin. Further more, vaccine comprising **antibody** to DC-SIGNR may prevents entry of viruses into liver cells.

L33 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2009 ACS on STN

2004:419958 Document No. 141:156031 High and low affinity carbohydrate ligands revealed for murine SIGN-R1 by carbohydrate array and cell binding approaches, and differing specificities for SIGN-R3 and **langerin** . Galustian, Christine; Park, Chae Gyu; Chai, Wengang; Kiso, Makato; Bruening, Sandra A.; Kang, Young-Sun; Steinman, Ralph M.; Feizi, Ten (Glycosciences Laboratory, Imperial College London, Middlesex, HA1 3UJ, UK). International Immunology, 16(6), 853-866 (English) 2004. CODEN: INIMEN. ISSN: 0953-8178. Publisher: Oxford University Press.

AB The number of receptors of the 'C-type' lectin family is greater than previously thought with a considerable proportion on cells (dendritic cells and macrophages) critical for innate immunity. Establishing that they bind carbohydrates, unravelling and comparing details of their ligands is crucial for understanding the mol. basis of the cell-cell and cell-pathogen interactions that they mediate. Here we use carbohydrate arrays as a new approach to discovering the ligands of three recently described C-type lectin-type receptors on antigen-presenting cells: murine SIGN-R1, SIGN-R3 and **langerin**. The arrays encompass an extensive panel including polysaccharides, glycoproteins, oligosaccharides and monosaccharides. These are probed with soluble forms of the receptors (IgG-Fc chimeras). The dominant specificities found for SIGN-R1 and SIGN-R3 are mannose- and fucose-related, as expressed on high mannose type N-glycans and Lewisa/b/Lewisx/y-type sequences, resp., with subtle differences between the receptors. The dominant specificity for **langerin** is unique so far: a Lewisx-related sequence with sulfate at position 6 of the terminal galactose. The polysaccharide dextran, known from classical studies to elicit a T-independent response, and whose cellular uptake has been shown recently to be mediated by membrane-associated SIGN-R1, gave no binding signals with the soluble form of the protein. We highlight here the addnl. need for cell-based assays for detecting biol. relevant low affinity ligands, for we show with SIGN-R1-transfected cells that dextran is such a low affinity ligand for SIGN-R1 that binding is detectable only with the cell membrane-associated receptor. But there is a close relationship between dextran recognition and mannose/fucose recognition, with dextran- and mannose-**conjugates** co-localizing in intracellular compartments.

L33 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2009 ACS on STN

2003:118018 Document No. 138:168835 Targeting of an antigen presenting cell

(APC) with a modulator of T cell signalling, such as a Notch ligand, coupled to the MHC class II-binding motif from a superantigen. Bodmer, Mark William; Champion, Brian Robert; McKenzie, Grahame James; Nye, Lucy Emma (Lorantis Limited, UK). PCT Int. Appl. WO 2003012111 A2 20030213, 93 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-GB3381 20020725. PRIORITY: GB 2001-18155 20010725.

AB The present invention relates to the concept of delivering a modulator of T cell signaling, such as a Notch ligand, to an antigen presenting cell (APC). The targeting approach disclosed uses, for example, the major histocompatibility complex (MHC) class II binding motif from a superantigen coupled to a modulator of the Notch signaling pathway. Superantigens bind both MHC class II mols. and subsets of T cell receptors and thus effectively cross-link APCs to T cells and activate cells polyclonally. The mol. regions of these mols. that impart T cell receptor (TCR) and MHC class II binding have been defined structurally and have been shown to be distinct regions of the mol. By using the MHC class II binding domain with a modulator of the Notch signaling pathway we can focus the activity of the Notch signaling pathway modulator to the APCs at the site of delivery. Further, the domain lacks toxin activity because it cannot find the T cell receptor to activate T cells. According to one aspect of the present invention there is provided a **conjugate** comprising a first and a second sequence wherein the first sequence comprises a polypeptide which is capable of binding to an APC, or a polynucleotide encoding therefor, and the second sequence comprises a polypeptide comprising a modulator of a signaling pathway in a T cell or a polynucleotide encoding therefor.

L33 ANSWER 7 OF 7 MEDLINE on STN DUPLICATE 3

2003121449. PubMed ID: 12603853. Cored tubules are present in human epidermal Langerhans cells. Lipsker Dan; Ziylan Umit; McDermott Ray; Spehner Daniele; Proamer Fabienne; Cazenave Jean-Pierre; Goud Bruno; de la Salle Henri; Salamero Jean; Hanau Daniel. (INSERM EP 99-08 Biologie des Cellules Dendritiques Humaines, Strasbourg, France.) The Journal of investigative dermatology, (2003 Mar) Vol. 120, No. 3, pp. 407-10. Journal code: 0426720. ISSN: 0022-202X. Pub. country: United States. Language: English.

AB Cored tubules are ultrastructural organelles described to date only in murine cells belonging to the Langerhans cell family and located in the dermis and its draining lymph nodes. These organelles, the function of which is unknown, differ from Birbeck granules and are interestingly not found in murine epidermal Langerhans cells. In this work we demonstrate that cored tubules are present in freshly isolated human epidermal Langerhans cells. The tubules were found to be interconnected with structures known to belong to the early endosomal pathway and could be immunolabeled with gold-**conjugated** anti-CD1a and anti-**Langerin** monoclonal **antibodies**, but only at 37 degrees C. At this temperature such **antibodies** are able to progress from the early sorting endosomes to the early recycling endosomes, which in human Langerhans cells include the Birbeck granules. These findings strongly suggest that cored tubules form part of the early recycling compartment.

=> s l2 and CD207

L34 13 L2 AND CD207

=> dup remove l34
PROCESSING COMPLETED FOR L34
L35 9 DUP REMOVE L34 (4 DUPLICATES REMOVED)

=> s l35 and targeting
L36 4 L35 AND TARGETING

=> dup remove l36
PROCESSING COMPLETED FOR L36
L37 4 DUP REMOVE L36 (0 DUPLICATES REMOVED)

=> d l37 1-4 cbib abs

L37 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2009 ACS on STN
2008:973996 Document No. 149:244360 Anti-DC-ASGPR **antibodies** **conjugated** with antigen for **targeting** antigen-presenting cell and enhancing antigen presentation against cancer and infection. Banchereau, Jacques F.; Oh, Sangkon; Zurawski, Gerard; Zurawski, Sandra; Li, Dapeng (Baylor Research Institute, USA). PCT Int. Appl. WO 2008097870 A2 20080814, 61pp. DESIGNATED STATES: W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, MT, NE, NL, NO, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2008-US52865 20080202. PRIORITY: US 2007-888036P 20070202.

AB The present invention includes compns. and methods for making and using DC-ASGPR or dendritic cell asialoglycoprotein receptor-specific **antibodies** or fragments that can, e.g., activate DCs and other cells.

L37 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2009 ACS on STN
2007:906284 Document No. 147:275679 Polypeptide **conjugates** of HLA-G histocompatibility antigens with ligand binding moieties and their transgenic expression in embryonic stem cells. Walsh, James (Axordia Limited, UK). PCT Int. Appl. WO 2007091078 A2 20070816, 93pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2007-GB448 20070208. PRIORITY: GB 2006-2688 20060210; GB 2006-5180 20060315.

AB Polypeptide **conjugates** comprising human histocompatibility antigen HLA-G fused to ligand binding moieties, such as single-chain variable fragment **antibody** derivs., enable the **targeting** of HLA-G to specific cell types and the use of the **conjugates** in the treatment of conditions that would benefit from the inhibition of T cell-mediated responses. The ectopic expression of HLA-G encoding nucleic acid mols. in human embryoic stem cells is also disclosed, and these transfected cells can be used to induce immune tolerance of the stem cells. A problem associated with gene therapy and/or tissue engineering is the provision of cell/tissue materials that do not induce a natural killer cell response in the recipient animal. The provision of stem cell lines that either constitutively express or developmentally express HLA-G genes

will facilitate procedures that involve gene and tissue replacement therapy.

L37 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2009 ACS on STN
2004:1126838 Document No. 142:73405 Vaccines comprising anti-DEC-205 **antibody**-antigen **conjugates** with or without dendritic cell maturation factor for enhancing long lasting antigen presentation or inducing tolerance. Hawiger, Daniel; Nussenzweig, Michel; Steinman, Ralph M.; Bonifaz, Laura (USA). U.S. Pat. Appl. Publ. US 20040258688 A1 20041223, 116 pp., Cont.-in-part of U.S. Ser. No. 925,284. (English). CODEN: USXXCO. APPLICATION: US 2004-800023 20040312. PRIORITY: US 1995-381528 19950131; WO 1996-US1383 19960131; US 2000-586704 20000605; US 2001-925284 20010809.

AB The present invention relates to methods for **targeting** antigen to antigen presenting cells through specific endocytic receptors, which results in persistent antigen presentation in the context of MHC mols. Such highly efficient antigen presentation results in robust and long lasting immune responses, in particular cell mediated responses. The invention provides for immune compns. containing **antibodies** to DEC-205 in combination with the antigen for eliciting either T cell mediated immunity when delivered with a dendritic cell maturation factor, or for inducing tolerance when delivered in the absence of a dendritic cell maturation factor. The antigen is tumor antigen or pathogenic antigen; and the dendritic cell maturation factor is anti-CD4 **antibody**, inflammatory cytokine, polyI/C, single stranded RNA, DNA, CpG, ligation of IL-1, TNF or TOLL-like receptor, TRAF-6 or NF-κB. The compns. described in the present invention are effective as a single dose at low concns. and show efficacy even with non-replicating subunit vaccines.

L37 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2009 ACS on STN
2003:118018 Document No. 138:168835 **Targeting** of an antigen presenting cell (APC) with a modulator of T cell signalling, such as a Notch ligand, coupled to the MHC class II-binding motif from a superantigen. Bodmer, Mark William; Champion, Brian Robert; McKenzie, Grahame James; Nye, Lucy Emma (Lorantis Limited, UK). PCT Int. Appl. WO 2003012111 A2 20030213, 93 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-GB3381 20020725. PRIORITY: GB 2001-18155 20010725.

AB The present invention relates to the concept of delivering a modulator of T cell signaling, such as a Notch ligand, to an antigen presenting cell (APC). The **targeting** approach disclosed uses, for example, the major histocompatibility complex (MHC) class II binding motif from a superantigen coupled to a modulator of the Notch signaling pathway. Superantigens bind both MHC class II mols. and subsets of T cell receptors and thus effectively cross-link APCs to T cells and activate cells polyclonally. The mol. regions of these mols. that impart T cell receptor (TCR) and MHC class II binding have been defined structurally and have been shown to be distinct regions of the mol. By using the MHC class II binding domain with a modulator of the Notch signaling pathway we can focus the activity of the Notch signaling pathway modulator to the APCs at the site of delivery. Further, the domain lacks toxin activity because it cannot find the T cell receptor to activate T cells. According to one aspect of the present invention there is provided a **conjugate** comprising a first and a second sequence wherein the first sequence comprises a polypeptide which is capable of binding to an APC, or a

polynucleotide encoding therefor, and the second sequence comprises a polypeptide comprising a modulator of a signaling pathway in a T cell or a polynucleotide encoding therefor.

=> s l2 and DC-SIGN
L38 51 L2 AND DC-SIGN

=> s l38 and targeting
L39 23 L38 AND TARGETING

=> dup remove l39
PROCESSING COMPLETED FOR L39
L40 11 DUP REMOVE L39 (12 DUPLICATES REMOVED)

=> d l40 1-11 cbib abs

L40 ANSWER 1 OF 11 CAPLUS COPYRIGHT 2009 ACS on STN
2008:410467 Document No. 148:401284 Compositions comprising antigen-presenting cell-**targeting** molecule or **antibody** for enhancing immunostimulation of adjuvant and antigen vaccine. Figdor, Carl Gustav; Bowdish, Katherine S.; Kretz-Rommel, Anke; Tacken, Paul J.; Faas McKnight, Susan (Alexion Pharmaceuticals, Inc., USA; Stichting Katholieke Universiteit). PCT Int. Appl. WO 2008039432 A1 20080403, 82pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, MT, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2007-US20634 20070924. PRIORITY: US 2006-847407P 20060926.
AB Provided herein are compns. and methods for enhancing an adjuvant effect. The methods involve **targeting** an adjuvant to an antigen presenting cell (APC) using a compound that binds to a cell surface marker (e.g. internalization receptor, C-type lectin or **DC-SIGN**) of an APC. Such methods are useful for stimulating an immune response in an animal, such as a human. Also provided are compns. that target an antigen and an adjuvant to an APC.

L40 ANSWER 2 OF 11 MEDLINE on STN DUPLICATE 1
2008327407. PubMed ID: 18490772. No advantage of cell-penetrating peptides over receptor-specific **antibodies** in **targeting** antigen to human dendritic cells for cross-presentation. Tacken Paul J; Joosten Ben; Reddy Anita; Wu Dayang; Eek Annemarie; Laverman Peter; Kretz-Rommel Anke; Adema Gosse J; Torensma Ruurd; Figdor Carl G. (Department of Tumor Immunology, Nijmegen Centre for Molecular Life Sciences, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.) Journal of immunology (Baltimore, Md. : 1950), (2008 Jun 1) Vol. 180, No. 11, pp. 7687-96. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.
AB Induction of CTL responses by dendritic cell (DC)-based vaccines requires efficient DC-loading strategies for class I Ags. Coupling Ags to cell-penetrating peptides (CPPs) or receptor-specific Abs improves Ag loading of DCs. In contrast to CPPs, receptor-specific Abs deliver **conjugated** Ags to DCs with high specificity, which is advantageous for in vivo strategies. It has, however, been speculated that CPPs facilitate uptake and endosomal escape of **conjugated** Ags, which would potently enhance cross-presentation. In this study, we directly compare the in vitro **targeting** efficiency of a humanized D1 Ab

directed against the human DC surface receptor **DC-SIGN** hD1 to that of three CPPs. The three CPPs colocalized within endosomes when targeted to human monocyte-derived DCs simultaneously, whereas hD1 was present in a different set of endosomes. However, within 75 min after uptake CPPs and hD1 colocalized extensively within the lysosomal compartment. Ab-mediated **targeting** of class I-restricted peptides to **DC-SIGN** enhanced cross-presentation of the peptides, while only one of the CPPs enhanced peptide presentation. This CPP and hD1 enhanced cross-presentation with equal efficiencies. Thus, we found no evidence of CPP specifically favoring the delivery of **conjugated** Ag to the DC class I presentation pathway. Given the specificity with which Abs recognize their targets, this favors the use of DC receptor-specific Abs for in vivo vaccination strategies.

L40 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2009 ACS on STN
2007:150261 Document No. 146:235877 Bacteriophage vectors comprising a modified lambda phage and a phage-encoded antigen for targeted delivery to antigen-presenting cells, and immunization uses. Dewhurst, Stephen; Gorman-Zanghi, Christine N.; Richards Gunzler, Julie (University of Rochester, USA). PCT Int. Appl. WO 2007015704 A2 20070208, 137 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-US35428 20051005. PRIORITY: US 2004-623743P 20041029.

AB Provided herein are modified phage surface polypeptides, phages with modified surface polypeptides, nucleic acids that encode the modified surface polypeptides, and related vectors and phages comprising the vectors. The provided phage surface polypeptides optionally comprise one or more modifications, including, for example, one or more modifications to enhance **targeting** to an antigen-presenting cell and one or more modifications that destabilize a viral capsid. Further provided herein are methods of making a lambda phage with a modified surface polypeptide and methods of making a lambda phage with a plurality of modified surface polypeptides. The surface polypeptide of the lambda phage can be gpD or gpV, there modified forms and fusion products with an integrin-binding **targeting** peptide and a peptide transduction domain (PTD), such as HIV-1 Tat PTD. Also provided herein are antigen delivery systems comprising the modified phages of the invention and methods of promoting an antigenic response in a subject by administering to the subject the antigen delivery system of the invention, alone or in combination with other immunization modalities. Provided are sequences for Escherichia-coli-codon-optimized variants of coliphage λ gpD and gpV genes, as well as a plasmid vector pTrc-gpD-ZZ-CO expressing gpD fusion protein. It was demonstrated, that lambda phage elicits an immune response to a phage-encoded antigen in mice.

L40 ANSWER 4 OF 11 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
2007:699715 The Genuine Article (R) Number: 172PK. **Antibody** -targeted vaccines.
Keler, T. (Reprint). Celldex Therapeut Inc, 222 Cameron Dr, Suite 400, Phillipsburg, NJ 08865 USA (Reprint). He, L.; Ramakrishna, V.; Champion, B.. Celldex Therapeut Inc, Phillipsburg, NJ 08865 USA; Celldex Therapeut Ltd, Cambridge, England. E-mail: tkeler@celldextherapeutics.com.
ONCOGENE (MAY 2007) Vol. 26, No. 25, pp. 3758-3767. ISSN: 0950-9232.
Publisher: NATURE PUBLISHING GROUP, MACMILLAN BUILDING, 4 CRINAN ST,

LONDON N1 9XW, ENGLAND. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The specificity and high affinity binding of **antibodies** provides these molecules with ideal properties for delivering a payload to target cells. This concept has been commercialized for cancer therapies using toxin- or radionucleotide-**conjugated antibodies** that are designed to selectively deliver cytotoxic molecules to cancer cells. Exploiting the same effective characteristics of **antibodies**, **antibody**-targeted vaccines (ATV) are designed to deliver disease-specific antigens to professional antigen-presenting cells (APCs), thus enabling the host's immune system to recognize and eliminate malignant or infected cells through adaptive immunity. The concept of ATVs has been in development for many years, and recently has entered clinical trials. Early studies with ATVs focused on the ability to induce humoral immunity in the absence of adjuvants. More recently, ATVs targeted to C-type lectin receptors have been exploited for induction of potent helper and cytolytic T-cell responses. To maximize their stimulatory capacity, the ATVs are being evaluated with a variety of adjuvants or other immunostimulatory agents. In the absence of co-administered immunostimulatory signals, APC-**targeting** can induce antigen-specific tolerance and, thus, may also be exploited in developing specific treatments for autoimmune and allergic diseases, or for preventing transplant rejection. The successful clinical application of this new class of **antibody**-based products will clearly depend on using appropriate combinations with other strategies that influence the immune system.

L40 ANSWER 5 OF 11 MEDLINE on STN DUPLICATE 2

2007610529. PubMed ID: 17893564. In vivo **targeting** of antigens to human dendritic cells through **DC-SIGN** elicits stimulatory immune responses and inhibits tumor growth in grafted mouse models. Kretz-Rommel Anke; Qin Fenghua; Dakappagari Naveen; Torensma Ruurd; Faas Susan; Wu Dayang; Bowdish Katherine S. (Alexion Antibody Technologies, Inc, San Diego, CA 92121, USA.) Journal of immunotherapy (Hagerstown, Md. : 1997), (2007 Oct) Vol. 30, No. 7, pp. 715-26. Journal code: 9706083. ISSN: 1524-9557. Pub. country: United States. Language: English.

AB Multiple cancer vaccine trials have been carried out using ex vivo generated autologous dendritic cells (DCs) loaded with tumor antigen before readministration into patients. Though promising, overall immunologic potency and clinical efficacy might be improved with more efficient DC-based therapies that avoid ex vivo manipulations, but are instead based on in vivo **targeting** of DCs. For initial in vivo proof of concept studies, we evaluated **targeting** of proteins or peptides to DCs through DC-specific intercellular adhesion molecule 3-grabbing nonintegrin (**DC-SIGN**). Because the biology of **DC-SIGN** is different between mice and humans, we assess human **DC-SIGN targeting** in the setting of elements of a human immune system in a mouse model. Administration of anti-**DC-SIGN antibodies** carrying either tetanus toxoid peptides or keyhole limpet hemocyanin (KLH) to Rag2gammaC mice reconstituted with human immune cells raised stimulatory human T-cell responses to the respective antigen without additional adjuvant requirements. Furthermore, administration of anti-**DC-SIGN antibody**-KLH **conjugate** enhanced the adjuvant properties of KLH resulting in inhibition of RAJI (Human Burkitt's Lymphoma Cell Line) cell tumor growth in Nonobese Diabetic/Severe Combined Immunodeficient mice transplanted with human immune cells. Thus, mouse models reconstituted with human immune cells seem to be suitable for evaluating DC-targeted vaccines, and furthermore, **targeting** to DCs in situ via **DC-SIGN** may provide a promising vaccine platform for inducing strong immune responses

against cancer and infectious disease agents.

L40 ANSWER 6 OF 11 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
2007210037 EMBASE Lewis X oligosaccharides **targeting** to **DC-SIGN** enhanced antigen-specific immune response.
Wang, Jingxue; Wei, Jing; Zhang, Xiaoping; Zhang, Bei; Zou, Wei; Wang, Yiqin; Mou, Zhirong; Ni, Bin; Wu, Yuzhang (correspondence). Institute of Immunology PLA, Third Military Medical University, GaoTanyan 30#, District ShaPingba, Chongqing, 400038, China. wuyuzhang@yahoo.com; jingxue.wang@hotmail.com. Zhang, Yongmin; Zhu, Zhenyuan. Ecole Normale Superieure, Departement de Chimie, CNRS UMR 8642, Paris, France. Zhu, Zhenyuan. College of Food Science and Biotechnology, Tianjin University of Science Technology, Tianjin, 300457, China.
Immunology Vol. 121, No. 2, pp. 174-182 Jun 2007.
Refs: 35.
ISSN: 0019-2805. E-ISSN: 1365-2567. CODEN: IMMUAM.
Pub. Country: United Kingdom. Language: English. Summary Language: English.
Entered STN: 20070521. Last Updated on STN: 20070521
AB Dendritic cell-specific intercellular-adhesion-molecule-grabbing non-integrin (**DC-SIGN**) is a potential target receptor for vaccination purposes. In the present study, we employed Lewis X (Le(x)) oligosaccharides, which mimic natural ligands, to target ovalbumin (OVA) to human dendritic cells (DCs) via **DC-SIGN**, to investigate the effect of this **DC-SIGN-targeting** strategy on the OVA-specific immune response. We demonstrated that Le(x) oligosaccharides could enhance the OVA-specific immune response as determined by enzyme-linked immunospot assay (ELISPOT), intracellular interferon-γ staining and (51)Cr-release assay. An almost 300-fold lower dose of Le(x)-OVA induced balanced interferon-γ-secreting cells compared to OVA alone. Furthermore, secretion of interleukin-10, a reported mediator of immune suppression related to **DC-SIGN**, was not increased by Le(x)-OVA, either alone or together with sCD40L-stimulated groups. A blocking **antibody** against **DC-SIGN** (12507) reduced the numbers of interferon-γ-secreting cells during Le(x)-OVA stimulation, yet it did not prevent Le (x) oligosaccharides from promoting the secretion of interleukin-10 that was induced by ultra-pure lipopolysaccharide. These results suggested that the strategy of **DC-SIGN targeting** mediated by Le(x) oligosaccharides could promote a T-cell response. This DC-**targeting** may imply a novel vaccination strategy. .COPYRGT. 2007 Blackwell Publishing Ltd.

L40 ANSWER 7 OF 11 CAPLUS COPYRIGHT 2009 ACS on STN
2005:843044 Document No. 143:265106 Effective induction of naive and recall T-cell responses by **targeting** antigen to human dendritic cells via a humanized anti-**DC-SIGN antibody**.
Tacken, Paul J.; de Vries, I. Jolanda M.; Gijzen, Karlijn; Joosten, Ben; Wu, Dayang; Rother, Russell P.; Faas, Susan J.; Punt, Cornelis J. A.; Torensma, Ruurd; Adema, Gosse J.; Figdor, Carl G. (Departments of Tumor Immunology, Pediatric Oncology, Nijmegen Centre for Molecular Life Sciences (NCMLS), Radboud University Nijmegen Medical Centre, Nijmegen, Neth.). Blood, 106(4), 1278-1285 (English) 2005. CODEN: BLOOAW. ISSN: 0006-4971. Publisher: American Society of Hematology.
AB Current dendritic cell (DC)-based vaccines are based on ex vivo-generated autologous DCs loaded with antigen prior to readministration into patients. A more direct and less laborious strategy is to target antigens to DCs in vivo via sp. surface receptors. Therefore, the authors developed a humanized **antibody**, hD1V1G2/G4 (hD1), directed against the C-type lectin DC-specific intercellular adhesion mol.

3-grabbing non-integrin (**DC-SIGN**) to explore its capacity to serve as a target receptor for vaccination purposes. HD1 was cross-linked to a model antigen, keyhole limpet hemocyanin (KLH). The authors observed that the chimeric **antibody**-protein complex (hD1-KLH) bound specifically to **DC-SIGN** and was rapidly internalized and translocated to the lysosomal compartment. To determine the **targeting** efficiency of hD1-KLH, monocyte-derived DCs and peripheral blood lymphocytes (PBLs) were obtained from patients who had previously been vaccinated with KLH-pulsed DCs. Autologous DCs pulsed with hD1-KLH induced proliferation of patient PBLs at a 100-fold lower concentration than KLH-pulsed DCs. In addition, hD1-KLH-targeted DCs induced proliferation of naive T cells recognizing KLH epitopes in the context of major histocompatibility complex (MHC) classes I and II. The authors conclude that **antibody**-mediated **targeting** of antigen to DCs via **DC-SIGN** effectively induces antigen-specific naive as well as recall T-cell responses. This identifies **DC-SIGN** as a promising target mol. for DC-based vaccination strategies.

L40 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2009 ACS on STN

2004:1012845 Document No. 142:91857 NK cell activation by dendritic cells (DCs) requires the formation of a synapse leading to IL-12 polarization in DCs. Borg, Christophe; Jalil, Abdelali; Laderach, Diego; Maruyama, Kouji; Wakasugi, Hiro; Charrier, Sabine; Ryffel, Bernhard; Cambi, Alessandra; Figdor, Carl; Vainchenker, William; Galy, Anne; Caignard, Anne; Zitvogel, Laurence (ERM0208 institut National de la Sante et de la Recherche Medicale (INSERM), Department of Clinical Biology, Institut Gustave Roussy, Villejuif, Fr.). Blood, 104(10), 3267-3275 (English) 2004. CODEN: BLOOAW. ISSN: 0006-4971. Publisher: American Society of Hematology.

AB Mature dendritic cells (mDCs) can trigger the effector functions of natural killer (NK) cells. Knock-out, small-interfering RNA or neutralizing **antibodies targeting** interleukin 12 (IL-12) subunits revealed a critical role for IL-12 in NK cell interferon γ (IFN-γ) secretion promoted by mDCs. However, NK cell activation by DCs also required direct cell-to-cell contacts. DC-mediated NK cell activation involved the formation of stimulatory synapses between DCs and NK cells. The formation of DC/NK cell **conjugates** depended on cytoskeleton remodeling and lipid raft mobilization in DCs. Moreover, the disruption of the DC cytoskeleton using pharmacol. agents or the loss-of-function mutation of the Wiskott-Aldrich syndrome protein abolished the DC-mediated NK cell activation. Synapse formation promoted the polarized secretion of preassembled stores of IL-12 by DCs toward the NK cell. The synaptic delivery of IL-12 by DCs was required for IFN-γ secretion by NK cells, as assessed using inhibitors of cytoskeleton rearrangements and Transwell expts. Therefore, the cross-talk between DCs and NK cells is dictated by functional synapses.

L40 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2009 ACS on STN

2003:118018 Document No. 138:168835 **Targeting** of an antigen presenting cell (APC) with a modulator of T cell signalling, such as a Notch ligand, coupled to the MHC class II-binding motif from a superantigen. Bodmer, Mark William; Champion, Brian Robert; McKenzie, Grahame James; Nye, Lucy Emma (Lorantis Limited, UK). PCT Int. Appl. WO 2003012111 A2 20030213, 93 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2.

APPLICATION: WO 2002-GB3381 20020725. PRIORITY: GB 2001-18155 20010725.

AB The present invention relates to the concept of delivering a modulator of T cell signaling, such as a Notch ligand, to an antigen presenting cell (APC). The **targeting** approach disclosed uses, for example, the major histocompatibility complex (MHC) class II binding motif from a superantigen coupled to a modulator of the Notch signaling pathway. Superantigens bind both MHC class II mols. and subsets of T cell receptors and thus effectively cross-link APCs to T cells and activate cells polyclonally. The mol. regions of these mols. that impart T cell receptor (TCR) and MHC class II binding have been defined structurally and have been shown to be distinct regions of the mol. By using the MHC class II binding domain with a modulator of the Notch signaling pathway we can focus the activity of the Notch signaling pathway modulator to the APCs at the site of delivery. Further, the domain lacks toxin activity because it cannot find the T cell receptor to activate T cells. According to one aspect of the present invention there is provided a **conjugate** comprising a first and a second sequence wherein the first sequence comprises a polypeptide which is capable of binding to an APC, or a polynucleotide encoding therefor, and the second sequence comprises a polypeptide comprising a modulator of a signaling pathway in a T cell or a polynucleotide encoding therefor.

L40 ANSWER 10 OF 11 MEDLINE on STN DUPLICATE 3

2003194873. PubMed ID: 12713687. Rapid monoclonal **antibody** generation via dendritic cell **targeting** in vivo. Berry Jody D; Licea Alexei; Popkov Mikhail; Cortez Xochitl; Fuller Roberta; Elia Marikka; Kerwin Lisa; Kubitz Diane; Barbas Carlos F 3rd. (The Skaggs Institute for Chemical Biology, The Scripps Research Institute, BCC-515, 10550 North Torrey Pines Road, La Jolla, CA 92126, USA.) Hybridoma and hybridomics, (2003 Feb) Vol. 22, No. 1, pp. 23-31. Journal code: 101131136. ISSN: 1536-8599. Pub. country: United States. Language: English.

AB Dendritic cells (DC) are the professional antigen-presenting cells of the immune system. Previous studies have demonstrated that **targeting** foreign antigens to DC leads to enhanced antigen (Ag)-specific responses in vivo. However, the utility of this strategy for the generation of MAbs has not been investigated. To address this question we immunized mice with IgG-peptide **conjugates** prepared with the hamster anti-murine CD11c MAb N418. Synthetic peptides corresponding to two different exposed regions of DC-specific ICAM-3 grabbing nonintegrin (**DC-SIGN**), a human C-type lectin, were **conjugated** to N418 using thiol-based chemistry. The N418 MAb served as the **targeting** molecule and synthetic peptides as the Ag (MAb-Ag). A rapid and peptide specific serum IgG response was produced by Day 7 when the synthetic peptides were linked to the N418 MAb, compared to peptide co-delivered with the N418 without linkage. Spleen cells from N418-peptide immunized mice were fused on Day 10, and three IgG1/k monoclonal **antibodies** (MAbs) were selected to one of the peptide epitopes (MID-peptide). One of the MAbs, Novik 2, bound to two forms of recombinant **DC-SIGN** protein in enzyme-linked immunosorbent assay (ELISA), and was specifically inhibited by the MID-peptide in solution. Two of these MAbs show specific binding to **DC-SIGN** expressed by cultured human primary DC. We conclude that in vivo DC **targeting** enhances the immunogenicity of synthetic peptides and is an effective method for the rapid generation of MAbs to predetermined epitopes.

L40 ANSWER 11 OF 11 CAPLUS COPYRIGHT 2009 ACS on STN

2000:756506 Document No. 133:321001 Bifunctional agents for immobilization of viruses to mucosa-colonizing bacteria. Lee, Peter P. (Osel, Inc., USA). PCT Int. Appl. WO 2000062758 A1 20001026, 42 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN,

CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US10079 20000414. PRIORITY: US 1999-PV129722 19990416.

AB The author discloses methods and chimeric constructs for increasing the half-life of a virus-specific ligand on a mucosal membrane by modifying the ligand to bind to bacteria colonized on the mucosal membrane. In one example, a fusion protein directed to human rhinovirus is prepared from the extracellular portion of ICAM-1 and the C-terminal fragment of lysostaphin. In a second example, a chimeric **conjugate** is prepared by the crosslinking of sialic acid to a scFv **antibody** directed to bacterial peptidoglycan. In a third example, a construct is prepared from avidin complexes of biotinylated soluble CD4 and scFv **antibody** directed to bacterial S-layer proteins.

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L41 64 L2 AND CD68

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L42 8 L41 AND TARGETING

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PROCESSING COMPLETED FOR L42
L43 8 DUP REMOVE L42 (0 DUPLICATES REMOVED)

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L43 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2009 ACS on STN
2007:906284 Document No. 147:275679 Polypeptide **conjugates** of HLA-G histocompatibility antigens with ligand binding moieties and their transgenic expression in embryonic stem cells. Walsh, James (Axordia Limited, UK). PCT Int. Appl. WO 2007091078 A2 20070816, 93pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2007-GB448 20070208. PRIORITY: GB 2006-2688 20060210; GB 2006-5180 20060315.

AB Polypeptide **conjugates** comprising human histocompatibility antigen HLA-G fused to ligand binding moieties, such as single-chain variable fragment **antibody** derivs., enable the **targeting** of HLA-G to specific cell types and the use of the **conjugates** in the treatment of conditions that would benefit from the inhibition of T cell-mediated responses. The ectopic expression of HLA-G encoding nucleic acid mols. in human embryoic stem cells is also disclosed, and these transfected cells can be used to induce immune tolerance of the stem cells. A problem associated with gene therapy and/or tissue engineering is the provision of cell/tissue materials that do not induce a natural killer cell response in the recipient animal. The provision of stem cell lines that either constitutively express or developmentally express HLA-G genes will facilitate procedures that involve gene and tissue replacement therapy.

L43 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2009 ACS on STN
2006:436832 Document No. 144:447261 Methods of detection and therapy for atheromatous plaques using immune modulation. Tawakol, Ahmed; Hamblin, Michael R.; Migrino, Raymond Q.; Gelfand, Jeffrey (The General Hospital Corporation, USA). PCT Int. Appl. WO 2006049599 A1 20060511, 94 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-US35849 20041028.

AB The present invention relates to methods for the detection and therapy of active atheromatous plaques, and in particular vulnerable plaques, whereby immune modulators are used to increase the uptake of diagnostic or therapeutic compns. by the inflammatory cells associated with such plaques. An example of a photosensitizer composition for **targeting** to macrophages of a vulnerable plaque is chlorin e6 **conjugated** to maleylated albumin. GM-CSF is an example of an immunomodulator which enhances detection of active atheromatous and vulnerable plaque.

L43 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2009 ACS on STN
2006:319578 Document No. 144:327043 Detection and therapy of vulnerable plaque with fluorescent and/or radiolabeled compositions. Fischman, Alan; Hamblin, Michael R.; Tawakol, Ahmed; Hasan, Tayyaba; Muller, James; Anderson, Rox; Elmaleh, David; Gewirtz, Henry (The General Hospital Corporation, USA). U.S. Pat. Appl. Publ. US 20060073100 A1 20060406, 52 pp., Cont.-in-part of U.S. Ser. No. 163,744. (English). CODEN: USXXCO. APPLICATION: US 2002-216026 20020809. PRIORITY: US 2002-163744 20020604; US 2002-365673P 20020315; US 2001-295627P 20010604.

AB The present invention relates to methods for selectively **targeting** Photodynamic Therapy ("PDT") to inflammatory components of vulnerable plaques. As such, the present invention provides methods for the identification of vulnerable plaques, using fluorescent compns., which include photosensitizer compns., and/or radiolabeled compds., as well as methods to treat vulnerable plaques by selectively **targeting** and/or eliminating the inflammatory components of vulnerable plaques.

L43 ANSWER 4 OF 8 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN
2005:457964 Document No.: PREV200510252432. Human bone marrow derived hematopoietic stem cells target and rescue degenerating retinal vasculature and neurons. Otani, A. [Reprint Author]; Dorrell, M. I.; Moreno, S.; Trombley, J.; Friedlander, M.. Scripps Res Inst, La Jolla, CA USA. IOVS, (APR 2004) Vol. 45, No. Suppl. 2, pp. U491.
Meeting Info.: Annual Meeting of the Association-for-Research-in-Vision-and-Ophthalmology. Ft Lauderdale, FL, USA. April 24 -29, 2004. Assoc Res Vis & Ophthalmol.
CODEN: IOVSDA. ISSN: 0146-0404. Language: English.

AB Purpose: We have previously reported that bone marrow (BM) derived lineage minus hematopoietic stem cells (Lin- HSC) have both vasculo- and neurotrophic effects after intravitreal injection eyes. In this study we demonstrate that similar populations of cells exist in human (BM) and exhibit similar rescue properties when injected into the eyes of SCID mice with retinal degeneration.Methods: Human BM (hBM) mononuclear cells were obtained from BM of healthy volunteers. To isolate a Lin- cell population from hBM mononuclear cells, the following **antibodies** were used with MACS separation system; CD2, 3, 4, 11a, 11b, 14, 16, 19, 33, 38, 45RA, 64, 68, 86, 235a (Pharmingen). To visualize the injected human cells, cells were labeled with dye (cell tracker green CMFDA, Molecular Probes) before injection. Cells (approximately 5x105/0.5 mu l) were

injected intravitreally into rd1/rd1 mice using a 33-gauge needled-syringe (Hamilton). To increase the accuracy of data, we injected Lin- cells into one eye and control cells into the contralateral eye in the same animal and compared the effect. Retinas were harvested at various time points, fixed and then stained with lectin or **antibodies** to CD31 followed by Alexa 488 or 594 **conjugated** secondary **antibodies**. Vascular images were obtained using a BioRad MP2100 confocal microscope equipped with a Spectra-Physics Tsunami Ti:sapphire laser and Lasersharp Software.Results: The injected hLin- HSC migrated to and targeted sites of retinal angiogenesis in a fashion identical to that observed when mouse Lin-HSC were injected. In addition to the vascular **targeting**, the human stem cells also provideda robust rescue effect on both the vascular and neuronal cell layers of the rd1/rd1 mice.Conclusions: These results confirm the presence of cells in hBM that target retinal vasculature and can prevent its degeneration in mice with inherited retinal degeneration. While several recent reports have described partial phenotypic rescue in mice and dogs with retinal degeneration after viral based gene therapy with the wild type gene, this is the first report of a cell based therapeutic effect achieved by vascular rescue with human cells.

L43 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2009 ACS on STN

2003:757448 Document No. 139:273196 Methods and devices for detection and therapy of atheromatous plaque. Fischman, Alan; Hamblin, Michael R.; Tawakol, Ahmed; Hasan, Tayyaba; Muller, James; Anderson, Rox; Elmaleh, David R.; Daghighian, Farhad (The General Hospital Corporation, USA). PCT Int. Appl. WO 2003077723 A2 20030925, 139 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US38852 20021203. PRIORITY: US 2002-365673P 20020315; US 2002-163744 20020604; US 2002-215600 20020809; US 2002-215958 20020809; US 2002-216026 20020809.

AB The present invention relates to devices for detection and therapy of active atheromatous plaque and/or thin-capped fibro-atheroma ('vulnerable plaque'), using selectively targeted fluorescent, radiolabeled, or fluorescent and radiolabeled compns. The present invention further relates to methods and devices for detection and therapy of active atheromatous plaques and/or vulnerable plaques, using selectively targeted compns., optionally comprising fluorescent and/or radiolabeled compns. An apparatus for detecting plaque in a blood vessel comprises a light emitter emitting light of a first wavelength and a light detector detecting light of a second wavelength; whereby a fluorescent composition is administered to the blood vessel, the fluorescent composition localizes to the plaque, and light of the first wavelength causes the fluorescent composition localized to the plaque to emit light having the second wavelength. The light emitter and light detector are included in a probe which is inserted into the blood vessel. A photosensitizer comprising chlorin e6 coupled to maleylated bovine serum albumin was prepared and was shown to accumulate in macrophage-rich plaques of an animal model system analogous to vulnerable plaques in humans. An intravascular fluorescence catheter was efficiently localized to vulnerable plaque in a rabbit coronary artery and was then used to illuminate the plaque with light activating the chlorin e6 for photodynamic therapy.

L43 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2009 ACS on STN

2003:118018 Document No. 138:168835 **Targeting** of an antigen presenting cell (APC) with a modulator of T cell signalling, such as a

Notch ligand, coupled to the MHC class II-binding motif from a superantigen. Bodmer, Mark William; Champion, Brian Robert; McKenzie, Grahame James; Nye, Lucy Emma (Lorantis Limited, UK). PCT Int. Appl. WO 2003012111 A2 20030213, 93 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-GB3381 20020725. PRIORITY: GB 2001-18155 20010725.

AB The present invention relates to the concept of delivering a modulator of T cell signaling, such as a Notch ligand, to an antigen presenting cell (APC). The **targeting** approach disclosed uses, for example, the major histocompatibility complex (MHC) class II binding motif from a superantigen coupled to a modulator of the Notch signaling pathway. Superantigens bind both MHC class II mols. and subsets of T cell receptors and thus effectively cross-link APCs to T cells and activate cells polyclonally. The mol. regions of these mols. that impart T cell receptor (TCR) and MHC class II binding have been defined structurally and have been shown to be distinct regions of the mol. By using the MHC class II binding domain with a modulator of the Notch signaling pathway we can focus the activity of the Notch signaling pathway modulator to the APCs at the site of delivery. Further, the domain lacks toxin activity because it cannot find the T cell receptor to activate T cells. According to one aspect of the present invention there is provided a **conjugate** comprising a first and a second sequence wherein the first sequence comprises a polypeptide which is capable of binding to an APC, or a polynucleotide encoding therefor, and the second sequence comprises a polypeptide comprising a modulator of a signaling pathway in a T cell or a polynucleotide encoding therefor.

L43 ANSWER 7 OF 8 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN

2001081553 EMBASE Hepatic veno-occlusive disease in two patients with relapsed acute myeloid leukemia treated with anti-CD33 calicheamicin (CMA-676) immunoconjugate.

Neumeister, P. (correspondence); Eibl, M.; Zinke-Cerwenka, W.; Scarpatetti, M.; Sill, H.; Linkesch, W.. Institute of Cancer Genetics, Columbia University, 1150 St. Nicholas Ave, New York, NY 10032, United States. peter.neumeister@gmx.at.

Annals of Hematology Vol. 80, No. 2, pp. 119-120 2001.

Refs: 11.

ISSN: 0939-5555. CODEN: ANHEE8.

Pub. Country: Germany. Language: English. Summary Language: English.

Entered STN: 20010316. Last Updated on STN: 20010316

AB Monoclonal **antibodies** recognizing hematopoietic antigens are increasingly being used to target therapy directly at leukemic cells, with the aim of achieving sustained remission with little systemic toxicity. Administration of anti-CD33 calicheamicin immunoconjugate is commonly regarded as being safe, with only moderate systemic non-hematological side effects. We report on two cases of hepatic veno-occlusive disease in heavily pretreated patients presenting with relapsed acute myeloid leukemia (AML). Since significant liver toxicity prevented further specific therapy in both patients, we recommend that **antibody** therapy with anti-CD33 immunoconjugate should be applied with caution in patients presenting with risk factors for the development of hepatic veno-occlusive disease.

L43 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2009 ACS on STN

1999:9728 Document No. 130:49292 The use of mononuclear phagocytes for in

vivo imaging of hypoxic/ischemic tissue. Lewis, Claire Elizabeth (University of Sheffield, UK). PCT Int. Appl. WO 9857665 A2 19981223, 33 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-GB637 19980318. PRIORITY: GB 1997-5521 19970318.

AB The invention relates to the imaging, preferably of hypoxic or ischemic sites, using mononuclear phagocytes. Specifically, the migratory behavior of the mononuclear phagocytes is exploited with a view to **targeting** imaging agents to sites that mononuclear phagocytes penetrate.

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L44 39 L2 AND CD83

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L45 7 L44 AND TARGETING

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PROCESSING COMPLETED FOR L45
L46 7 DUP REMOVE L45 (0 DUPLICATES REMOVED)

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L46 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2009 ACS on STN

2008:1187820 Document No. 149:432694 Discrete size and shape specific organic nanoparticles designed to elicit an immune response. Desimone, Joseph M.; Petros, Robby; Frelinger, Jeffrey; Buntzman, Adam (The University of North Carolina, USA). PCT Int. Appl. WO 2008118861 A2 20081002, 78 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, MT, NE, NL, NO, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2008-US58022 20080324. PRIORITY: US 2007-919720P 20070323.

AB The authors disclose the preparation of organic nanoparticles using particle replication in non-wetting templates (PRINT) technol. and their application in the targeted delivery of **conjugated** agents to immune cells. In one example, the organic nanoparticles comprise polyethylene glycol hydrogels functionalized for surface conjugation of protein and non-protein antigens or detectable labels.

L46 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2009 ACS on STN

2008:973996 Document No. 149:244360 Anti-DC-ASGPR **antibodies** **conjugated** with antigen for **targeting** antigen-presenting cell and enhancing antigen presentation against cancer and infection. Banchereau, Jacques F.; Oh, Sangkon; Zurawski, Gerard; Zurawski, Sandra; Li, Dapeng (Baylor Research Institute, USA). PCT Int. Appl. WO 2008097870 A2 20080814, 61pp. DESIGNATED STATES: W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH,

PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, MT, NE, NL, NO, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2008-US52865 20080202. PRIORITY: US 2007-888036P 20070202.

AB The present invention includes compns. and methods for making and using DC-ASGPR or dendritic cell asialoglycoprotein receptor-specific **antibodies** or fragments that can, e.g., activate DCs and other cells.

L46 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2009 ACS on STN

2007:906284 Document No. 147:275679 Polypeptide **conjugates** of HLA-G histocompatibility antigens with ligand binding moieties and their transgenic expression in embryonic stem cells. Walsh, James (Axordia Limited, UK). PCT Int. Appl. WO 2007091078 A2 20070816, 93pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2007-GB448 20070208. PRIORITY: GB 2006-2688 20060210; GB 2006-5180 20060315.

AB Polypeptide **conjugates** comprising human histocompatibility antigen HLA-G fused to ligand binding moieties, such as single-chain variable fragment **antibody** derivs., enable the **targeting** of HLA-G to specific cell types and the use of the **conjugates** in the treatment of conditions that would benefit from the inhibition of T cell-mediated responses. The ectopic expression of HLA-G encoding nucleic acid mols. in human embryoic stem cells is also disclosed, and these transfected cells can be used to induce immune tolerance of the stem cells. A problem associated with gene therapy and/or tissue engineering is the provision of cell/tissue materials that do not induce a natural killer cell response in the recipient animal. The provision of stem cell lines that either constitutively express or developmentally express HLA-G genes will facilitate procedures that involve gene and tissue replacement therapy.

L46 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2009 ACS on STN

2006:566779 Document No. 145:26592 Combination immunotherapy and detection of inflammatory and immune-dysregulatory disease, infectious disease, pathologic angiogenesis and cancer. Goldenberg, David M.; Hansen, Hans J. (Immunomedics, Inc., USA). PCT Int. Appl. WO 2006063150 A2 20060615, 80 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-US44446 20051208. PRIORITY: US 2004-634076P 20041208.

AB The authors disclose combination therapy of inflammatory and immune-dysregulatory diseases using monospecific and multi-specific antagonists. The antagonists target: (i) proinflammatory effectors of the innate immune system, (ii) coagulation factors, and (iii) targets specifically associated with an inflammatory or immune-dysregulatory disorder, with a pathol. angiogenesis or cancer, or with an infectious disease, wherein the targets included in group (iii) are neither a

proinflammatory effector of the immune system nor a coagulation factor. In one example, treatment of septic shock is effected by administration of humanized **antibodies targeting** LPS and macrophage migration inhibitory factor in combination with activated protein C.

L46 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2009 ACS on STN
2005:977400 Document No. 143:265032 Targeted vaccine adjuvants based on modified cholera toxin. Lycke, Nils (Department of Clinical Immunology, University of Goeteborg, Goeteborg, S413 46, Swed.). Current Molecular Medicine, 5(6), 591-597 (English) 2005. CODEN: CMMUBP. ISSN: 1566-5240. Publisher: Bentham Science Publishers Ltd..
AB A review. The present review describes immunomodulation with targeted adjuvants that will allow for the development of efficacious mucosal vaccines. We have studied cholera toxin (CT) and derivs. thereof, to rationally design vaccine adjuvant vectors that are both highly efficacious as well as safe and non-toxic. Two strategies were exploited; the first using CT or the enzymically inactive receptor-binding B-subunit of CT (CTB) and the second, using CTA1 or an enzymically inactive mutant CTA1R7K., that was linked, in a fusion protein, to the B-cell **targeting** moiety, DD, from Staphylococcus areus protein A. Our studies provide compelling evidence that delivery of Ag in the absence of ADP-ribosylation can promote tolerance, whereas, ADP-ribosyltransferase-active **conjugates**, prevent tolerance but induce IgA immunity. Our anal. revealed unique subsets of mucosal and systemic DC that appeared to be responsible for the ADP-ribosyltransferase sensitive dichotomy between tolerance and IgA immunity. Whether **targeting** of B cells suffice for tolerance-induction or requires participation of DCs, is at present an unresolved issue. Nevertheless, enzymic modulation differentiates and matures the DC to promote CD4 T cell help for IgA B cell development. Ag-presentation in the absence of enzyme, as seen with CTA1R7K-DD, expands specific T cells to a similar extent as enzymically active CTA1-DD, but fails to recruit help for germinal center expansion of activated B cells. We have given special attention to the genes that adjuvants turn on using Affymetrix technol. In particular, modulation of the expression of co-stimulatory mols. on the targeted APC; CD80, CD86, **CD83** and B7RP-1, play important roles for the effect of the ADP-ribosylating CTA1-based adjuvants for the development of tolerance or active IgA immunity.

L46 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2009 ACS on STN
2004:857330 Document No. 141:348819 Targeted delivery of antigens in vaccines using MHC class I α3 **conjugates** with **antibodies** to cell surface markers. Zauderer, Maurice; Paris, Mark J.; Smith, Ernest S. (Vaccinex, Inc., USA). PCT Int. Appl. WO 2004087058 A2 20041014, 115 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-US9385 20040326. PRIORITY: US 2003-457896P 20030328.
AB A method of improving the efficiency of delivery of antigens for vaccine use to T cells is described. The antigen is delivered in a complex with the non-polymorphic α3 domain of a class I MHC antigen **conjugated** to an **antibody** to a cell surface marker; a β2-microglobulin, and a costimulatory mol. or cytokine. The α3 domain may be modified to improve binding to class I MHC α chains. The complexes of the invention are useful for treating and/or preventing cancer, infectious diseases, autoimmune diseases, and/or allergies.

L46 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2009 ACS on STN
2003:118018 Document No. 138:168835 **Targeting** of an antigen presenting cell (APC) with a modulator of T cell signalling, such as a Notch ligand, coupled to the MHC class II-binding motif from a superantigen. Bodmer, Mark William; Champion, Brian Robert; McKenzie, Grahame James; Nye, Lucy Emma (Lorantis Limited, UK). PCT Int. Appl. WO 2003012111 A2 20030213, 93 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-GB3381 20020725. PRIORITY: GB 2001-18155 20010725.
AB The present invention relates to the concept of delivering a modulator of T cell signaling, such as a Notch ligand, to an antigen presenting cell (APC). The **targeting** approach disclosed uses, for example, the major histocompatibility complex (MHC) class II binding motif from a superantigen coupled to a modulator of the Notch signaling pathway. Superantigens bind both MHC class II mols. and subsets of T cell receptors and thus effectively cross-link APCs to T cells and activate cells polyclonally. The mol. regions of these mols. that impart T cell receptor (TCR) and MHC class II binding have been defined structurally and have been shown to be distinct regions of the mol. By using the MHC class II binding domain with a modulator of the Notch signaling pathway we can focus the activity of the Notch signaling pathway modulator to the APCs at the site of delivery. Further, the domain lacks toxin activity because it cannot find the T cell receptor to activate T cells. According to one aspect of the present invention there is provided a **conjugate** comprising a first and a second sequence wherein the first sequence comprises a polypeptide which is capable of binding to an APC, or a polynucleotide encoding therefor, and the second sequence comprises a polypeptide comprising a modulator of a signaling pathway in a T cell or a polynucleotide encoding therefor.

=> s l2 and CD33
L47 647 L2 AND CD33

=> s l47 and targeting
L48 149 L47 AND TARGETING

=> s l48 and antigen presenting
L49 1 L48 AND ANTIGEN PRESENTING

=> d l49 cbib abs

L49 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2009 ACS on STN
2003:118018 Document No. 138:168835 **Targeting** of an **antigen presenting** cell (APC) with a modulator of T cell signalling, such as a Notch ligand, coupled to the MHC class II-binding motif from a superantigen. Bodmer, Mark William; Champion, Brian Robert; McKenzie, Grahame James; Nye, Lucy Emma (Lorantis Limited, UK). PCT Int. Appl. WO 2003012111 A2 20030213, 93 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT,

LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-GB3381 20020725. PRIORITY: GB 2001-18155 20010725.

AB The present invention relates to the concept of delivering a modulator of T cell signaling, such as a Notch ligand, to an **antigen presenting** cell (APC). The **targeting** approach disclosed uses, for example, the major histocompatibility complex (MHC) class II binding motif from a superantigen coupled to a modulator of the Notch signaling pathway. Superantigens bind both MHC class II mols. and subsets of T cell receptors and thus effectively cross-link APCs to T cells and activate cells polyclonally. The mol. regions of these mols. that impart T cell receptor (TCR) and MHC class II binding have been defined structurally and have been shown to be distinct regions of the mol. By using the MHC class II binding domain with a modulator of the Notch signaling pathway we can focus the activity of the Notch signaling pathway modulator to the APCs at the site of delivery. Further, the domain lacks toxin activity because it cannot find the T cell receptor to activate T cells. According to one aspect of the present invention there is provided a **conjugate** comprising a first and a second sequence wherein the first sequence comprises a polypeptide which is capable of binding to an APC, or a polynucleotide encoding therefor, and the second sequence comprises a polypeptide comprising a modulator of a signaling pathway in a T cell or a polynucleotide encoding therefor.

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=> s l2 and CD54
L50        353 L2 AND CD54

=> s l50 and targeting
L51         39 L50 AND TARGETING

=> dup remove l51
PROCESSING COMPLETED FOR L51
L52         34 DUP REMOVE L51 (5 DUPLICATES REMOVED)

=> s l52 and Notch ligand
L53          1 L52 AND NOTCH LIGAND

=> d l53 cbib abs

L53  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2009 ACS on STN
2003:118018   Document No. 138:168835  Targeting of an antigen
     presenting cell (APC) with a modulator of T cell signalling, such as a
     Notch ligand, coupled to the MHC class II-binding motif
     from a superantigen.  Bodmer, Mark William; Champion, Brian Robert;
     McKenzie, Grahame James; Nye, Lucy Emma (Lorantis Limited, UK).  PCT Int.
     Appl. WO 2003012111 A2 20030213, 93 pp.  DESIGNATED STATES: W:  AE, AG,
     AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ,
     DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN,
     IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK,
     MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL,
     TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE,
     BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT,
     LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR.  (English).  CODEN:
     PIXXD2.  APPLICATION: WO 2002-GB3381 20020725.  PRIORITY: GB 2001-18155
     20010725.
AB   The present invention relates to the concept of delivering a modulator of
     T cell signaling, such as a Notch ligand, to an
     antigen presenting cell (APC).  The targeting approach disclosed
     uses, for example, the major histocompatibility complex (MHC) class II
     binding motif from a superantigen coupled to a modulator of the Notch
     signaling pathway.  Superantigens bind both MHC class II mols. and subsets
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of T cell receptors and thus effectively cross-link APCs to T cells and activate cells polyclonally. The mol. regions of these mols. that impart T cell receptor (TCR) and MHC class II binding have been defined structurally and have been shown to be distinct regions of the mol. By using the MHC class II binding domain with a modulator of the Notch signaling pathway we can focus the activity of the Notch signaling pathway modulator to the APCs at the site of delivery. Further, the domain lacks toxin activity because it cannot find the T cell receptor to activate T cells. According to one aspect of the present invention there is provided a **conjugate** comprising a first and a second sequence wherein the first sequence comprises a polypeptide which is capable of binding to an APC, or a polynucleotide encoding therefor, and the second sequence comprises a polypeptide comprising a modulator of a signaling pathway in a T cell or a polynucleotide encoding therefor.

=> s l2 and "BDCA-2"
L54 4 L2 AND "BDCA-2"

=> dup remove l54
PROCESSING COMPLETED FOR L54
L55 4 DUP REMOVE L54 (0 DUPLICATES REMOVED)

=> s l55 and targeting
L56 2 L55 AND TARGETING

=> d l56 1-2 cbib abs

L56 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2009 ACS on STN
2008:973996 Document No. 149:244360 Anti-DC-ASGPR **antibodies** **conjugated** with antigen for **targeting** antigen-presenting cell and enhancing antigen presentation against cancer and infection. Banchereau, Jacques F.; Oh, Sangkon; Zurawski, Gerard; Zurawski, Sandra; Li, Dapeng (Baylor Research Institute, USA). PCT Int. Appl. WO 2008097870 A2 20080814, 61pp. DESIGNATED STATES: W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, MT, NE, NL, NO, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2008-US52865 20080202. PRIORITY: US 2007-888036P 20070202.
AB The present invention includes compns. and methods for making and using DC-ASGPR or dendritic cell asialoglycoprotein receptor-specific **antibodies** or fragments that can, e.g., activate DCs and other cells.

L56 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2009 ACS on STN
2003:118018 Document No. 138:168835 **Targeting** of an antigen presenting cell (APC) with a modulator of T cell signalling, such as a Notch ligand, coupled to the MHC class II-binding motif from a superantigen. Bodmer, Mark William; Champion, Brian Robert; McKenzie, Grahame James; Nye, Lucy Emma (Lorantis Limited, UK). PCT Int. Appl. WO 2003012111 A2 20030213, 93 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML,

MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2.
APPLICATION: WO 2002-GB3381 20020725. PRIORITY: GB 2001-18155 20010725.

AB The present invention relates to the concept of delivering a modulator of T cell signaling, such as a Notch ligand, to an antigen presenting cell (APC). The **targeting** approach disclosed uses, for example, the major histocompatibility complex (MHC) class II binding motif from a superantigen coupled to a modulator of the Notch signaling pathway. Superantigens bind both MHC class II mols. and subsets of T cell receptors and thus effectively cross-link APCs to T cells and activate cells polyclonally. The mol. regions of these mols. that impart T cell receptor (TCR) and MHC class II binding have been defined structurally and have been shown to be distinct regions of the mol. By using the MHC class II binding domain with a modulator of the Notch signaling pathway we can focus the activity of the Notch signaling pathway modulator to the APCs at the site of delivery. Further, the domain lacks toxin activity because it cannot find the T cell receptor to activate T cells. According to one aspect of the present invention there is provided a **conjugate** comprising a first and a second sequence wherein the first sequence comprises a polypeptide which is capable of binding to an APC, or a polynucleotide encoding therefor, and the second sequence comprises a polypeptide comprising a modulator of a signaling pathway in a T cell or a polynucleotide encoding therefor.

=> s l2 and "BDCA-3"
L57 5 L2 AND "BDCA-3"

=> dup remove l57
PROCESSING COMPLETED FOR L57
L58 2 DUP REMOVE L57 (3 DUPLICATES REMOVED)

=> d l58 1-2 cbib abs

L58 ANSWER 1 OF 2 MEDLINE on STN DUPLICATE 1
2009392944. PubMed ID: 19494282. The C-type lectin Clec12A present on mouse and human dendritic cells can serve as a target for antigen delivery and enhancement of **antibody** responses. Lahoud Mireille H; Proietto Anna I; Ahmet Fatma; Kitsoulis Susie; Eidsmo Liv; Wu Li; Sathe Priyanka; Pietersz Suzanne; Chang Hsuen-Wen; Walker Ian D; Maraskovsky Eugene; Braley Hal; Lew Andrew M; Wright Mark D; Heath William R; Shortman Ken; Caminschi Irina. (The Walter and Eliza Hall Institute of Medical Research, Parkville, Victoria, Australia.) Journal of immunology (Baltimore, Md. : 1950), (2009 Jun 15) Vol. 182, No. 12, pp. 7587-94. Journal code: 2985117R. E-ISSN: 1550-6606. Pub. country: United States. Language: English.

AB We have cloned the mouse and human C-type lectin Clec12A, expressed both, and produced mAb recognizing both. Mouse Clec12A is highly expressed on splenic CD8(+) dendritic cells (DC) and plasmacytoid DC. A proportion of CD8(-)DC also expresses lower levels of Clec12A, as do monocytes, macrophages, and B cells. Human CLEC12A, like the mouse counterpart, is expressed on blood monocytes and DC, including pDC and **BDCA-3**(+)DC, the proposed equivalent of mouse CD8(+)DC. To determine whether Ag targeted to Clec12A could induce immune responses, mice were injected with a rat mAb recognizing Clec12A, or a control rat mAb, then production of anti-rat Ig was measured. Anti-Clec12A mAb alone produced only moderate responses, but these were amplified by coinjecting only small amounts of LPS as a DC activation agent. Furthermore, when OVA was **conjugated** to anti-Clec12A mAb, OVA-specific T cells were induced to proliferate. This Ag presentation to naive T cells was due to targeting conventional DC, because their ablation eliminated T cell activation. The potent Ab responses induced using microgram amounts of anti-Clec12A and minimal amounts of adjuvant demonstrate that this

molecule can be used as an Ag-delivery target to enhance Ab responses to vaccines.

L58 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2009 ACS on STN
2003:118018 Document No. 138:168835 Targeting of an antigen presenting cell (APC) with a modulator of T cell signalling, such as a Notch ligand, coupled to the MHC class II-binding motif from a superantigen. Bodmer, Mark William; Champion, Brian Robert; McKenzie, Grahame James; Nye, Lucy Emma (Lorantis Limited, UK). PCT Int. Appl. WO 2003012111 A2 20030213, 93 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-GB3381 20020725. PRIORITY: GB 2001-18155 20010725.
AB The present invention relates to the concept of delivering a modulator of T cell signaling, such as a Notch ligand, to an antigen presenting cell (APC). The targeting approach disclosed uses, for example, the major histocompatibility complex (MHC) class II binding motif from a superantigen coupled to a modulator of the Notch signaling pathway. Superantigens bind both MHC class II mols. and subsets of T cell receptors and thus effectively cross-link APCs to T cells and activate cells polyclonally. The mol. regions of these mols. that impart T cell receptor (TCR) and MHC class II binding have been defined structurally and have been shown to be distinct regions of the mol. By using the MHC class II binding domain with a modulator of the Notch signaling pathway we can focus the activity of the Notch signaling pathway modulator to the APCs at the site of delivery. Further, the domain lacks toxin activity because it cannot find the T cell receptor to activate T cells. According to one aspect of the present invention there is provided a **conjugate** comprising a first and a second sequence wherein the first sequence comprises a polypeptide which is capable of binding to an APC, or a polynucleotide encoding therefor, and the second sequence comprises a polypeptide comprising a modulator of a signaling pathway in a T cell or a polynucleotide encoding therefor.

=> s l2 and "BDCA-4"
L59 4 L2 AND "BDCA-4"

=> dup remove l59
PROCESSING COMPLETED FOR L59
L60 4 DUP REMOVE L59 (0 DUPLICATES REMOVED)

=> s l60 and targeting
L61 1 L60 AND TARGETING

=> d l61 cbib abs

L61 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2009 ACS on STN
2003:118018 Document No. 138:168835 **Targeting** of an antigen presenting cell (APC) with a modulator of T cell signalling, such as a Notch ligand, coupled to the MHC class II-binding motif from a superantigen. Bodmer, Mark William; Champion, Brian Robert; McKenzie, Grahame James; Nye, Lucy Emma (Lorantis Limited, UK). PCT Int. Appl. WO 2003012111 A2 20030213, 93 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX,

MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2.
APPLICATION: WO 2002-GB3381 20020725. PRIORITY: GB 2001-18155 20010725.

AB The present invention relates to the concept of delivering a modulator of T cell signaling, such as a Notch ligand, to an antigen presenting cell (APC). The **targeting** approach disclosed uses, for example, the major histocompatibility complex (MHC) class II binding motif from a superantigen coupled to a modulator of the Notch signaling pathway. Superantigens bind both MHC class II mols. and subsets of T cell receptors and thus effectively cross-link APCs to T cells and activate cells polyclonally. The mol. regions of these mols. that impart T cell receptor (TCR) and MHC class II binding have been defined structurally and have been shown to be distinct regions of the mol. By using the MHC class II binding domain with a modulator of the Notch signaling pathway we can focus the activity of the Notch signaling pathway modulator to the APCs at the site of delivery. Further, the domain lacks toxin activity because it cannot find the T cell receptor to activate T cells. According to one aspect of the present invention there is provided a **conjugate** comprising a first and a second sequence wherein the first sequence comprises a polypeptide which is capable of binding to an APC, or a polynucleotide encoding therefor, and the second sequence comprises a polypeptide comprising a modulator of a signaling pathway in a T cell or a polynucleotide encoding therefor.

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---Logging off of STN---

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Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	437.38	437.60

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-47.56	-47.56

STN INTERNATIONAL LOGOFF AT 10:25:52 ON 11 AUG 2009